AL-TR-1991-0162

ARMSTRONG LABORATORY

PHARMACOKINETIC MODELING OF TRIVALENT AND HEXAVALENT CHROMIUM BASED ON INGESTION AND INHALATION OF SOLUBLE CHROMIUM COMPOUNDS

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DECEMBER 1991

FINAL REPORT FOR PERIOD JUNE 1990 THROUGH DECEMBER 1991

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AL-TR-1991-0162

The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

ERIK K. VERMULEN, Colonel, USAF, BSC
Director, Toxicology Division
Armstrong Laboratory

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave Blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	December 1991	Final Report, June 1990-December 1991

4. TITLE AND SUBTITLE Pharmacokinetic Modeling of Trivalent and Hexavalent Chromium Based on Ingestion and Inhalation of Soluble Chromium Compounds

5. FUNDING NUMBERS

Contract F33615-85-C-0532
PE 62202F
PR 6302
TA 630213
WU 63021302

6. AUTHOR(S)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

AL/OET
Armstrong Laboratory
Wright-Patterson AFB, OH 45433-6573

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

AL-TR-1991-0162

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

A physiologically-based model of chromium disposition in the rat has been developed. Absorption, distribution, and excretion of chromium are superimposed on a general physiological model of rat growth and development. The model considers both Cr (VI) and Cr (III), administered either orally or by inhalation. It incorporates reduction of Cr (VI) to Cr (III) in all tissues including the lung and the GI tract. Chromium is cleared from the lung by systemic absorption and by mucociliary clearance into the GI tract. Parameter values are based on literature data and on the results of a concurrent experimental study in which rats were given either Cr (III) or Cr (VI) either in the drinking water or by inhalation. Blood, tissue, urine, and fecal chromium levels were monitored on days 2, 5, 10, 20, and 40 of the 40-day exposure period, and at 20 days postexposure.

14. SUBJECT TERMS

Cr (VI), Cr (III), Oral exposure, Inhalation exposure, Physiologically based model

15. NUMBER OF PAGES

141

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	UL

PREFACE

This document serves as the final technical report describing the development of a physiologically based pharmacokinetic model of chromium disposition supported by collection of pharmacokinetic data after ingestion or inhalation of trivalent or hexavalent soluble chromium compounds. The research described herein began in June 1990 and was completed in December 1991 by the Department of Environmental Health, University of Cincinnati School of Medicine, under a subcontract to ManTech Environmental Technology, Inc., Toxic Hazards Research Unit (THRU), and was coordinated by Allen Vinegar, Ph.D., Manager of the Biological Simulation Program at the THRU.

This work was sponsored by the Toxicology Division, Occupational and Environmental Health Directorate, Armstrong Laboratory, and was performed under Department of the Air Force Contract No. F33615-85-C-0532, Study No. TH 0-20.8. Lt Col Michael B. Ballinger and Lt Col James N. McDougal, respectively, served as Contract Technical Monitor.

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I. SELECTIVE REVIEW OF CHROMIUM LITERATURE

A. BACKGROUND

Chromium is one of a group of metals that pose risk assessment issues related to form-specific biological activity. Chromium exists in several forms with distinct chemical and physical stabilities and toxicities (Grant and Mushak, 1989). Historically, the primary distinction has been between the two principal oxidation states, Cr(III) and Cr(VI). Differential solubilities of chromium compounds are also significant, particularly with regard to the relative potency of different inhaled hexavalent chromium compounds as causative agents for lung cancer (Langard, 1990).

Both Cr(III) and Cr(VI) form compounds that range from highly water soluble to essentially insoluble in water. Many of the chromium-containing compounds of industrial importance, such as the K, Na, and NH_4 chromates and dichromates, chromium trioxide (CrO_3), and the hydrated Cr(III) nitrate, chloride, acetate, and sulfate salts, are soluble or highly soluble in water. Some of the mixed salt chromate pigments are poorly soluble. Lead chromate, chromium oxide (Cr_2O_3), and chromic hydroxide ($Cr(OH)_3$) are poorly soluble or insoluble. This range of solubility behaviors has complicated efforts to evaluate chromium toxicity.

Soluble Cr(VI) salts will be absorbed from the lung and may cause systemic toxicity if not reduced to Cr(III). Insoluble Cr(VI) salts in the lung may be transported to the gut, where, if Cr(VI) has escaped reduction in the stomach, it can be absorbed. Reduction of Cr(VI) to Cr(III) occurs rapidly in nearly all tissues and biological fluids. Cr(III) does not cross membranes readily. It is poorly absorbed from the gastrointestinal tract, and historically it has not been considered to be toxic to any significant extent, partly because Cr(III) was believed to be excluded from the intracellular milieu. From this point of view, reduction of Cr(VI) to Cr(III) is a detoxification mechanism. The rapidity and essentially universal distribution of chromium reduction processes throughout the body have suggested to some the existence of a threshold in Cr(VI) dose-response relationships (Petrilli and DeFlora, 1988).

However, it is now known that Cr(III) can cross cell and other membranes when the ligand environment is favorable. Penetration of Cr(III) into tissues was at one time suggested to be due to trapping of colloidal chromium by the reticuloendothelial system (Kraintz and Talmage, 1952), but it is now believed that excretion of Cr(III) in bile and its appearance in erythrocytes and tissues are facilitated by formation of diffusible complexes (Bianchi and Levis, 1988; Norseth, 1988). Certainly the kinetics of different Cr(III) salts can be quite different, indicating that speciation is an important factor determining Cr(III) kinetic behavior (Visek et al., 1953).

More important with respect to the carcinogenic action of Cr(VI) in the lung (see next Section) is that several of the pathways for reduction of Cr(VI) have been shown to generate short-lived, chemically reactive intermediates. Reduction of Cr(VI) to Cr(III) must be considered an activation mechanism in this context.

B. TOXICITY

1. Carcinogenicity

Industrial exposures to chromium are associated principally with the manufacture of chromates, including chromate pigments; chromium electroplating, which generates aerosols of chromic acid containing chromium trioxide; production of chromium ferroalloys; and stainless steel welding. Chromate production, electroplating, and welding are associated primarily with exposure to soluble compounds of Cr(VI). Chromium ferroalloy production involves exposure to insoluble compounds presumed to be largely Cr(III) although some Cr(VI) exposure probably also occurs. Stainless-steel welders are exposed to nickel as well as to chromium compounds (Raithel et al., 1988), and chrome electroplaters may be also (Hathaway, 1989). Reviews of a large number of epidemiological studies of cohorts of workers employed in these industries have led to the conclusion that workers exposed to Cr(VI) as chromates, dichromates, or chromic trioxide are at risk for development of lung cancer (Langard et al., 1990). Evidence for an association of lung cancer with employment in production of ferrochromium alloys is weak, and it is not yet clear whether such as association exists (Langard et al., 1990). Similarly, data for respiratory cancer prevalence in welders are equivocal with respect to involvement of chromium, particularly since nickel in some chemical forms is an established lung carcinogen (Stern, 1983; Becker et al., 1985).

Animal studies have generally provided information only about the intrinsic carcinogenicity of chromium compounds, and not about the quantitative relationship of exposure to carcinogenic outcome. There is no evidence that metallic chromium powder or Cr(III) compounds are carcinogenic in animals by any route of administration (Gibb et al., 1988). Implantation-site tumors have been found in animals given Cr(VI) compounds intramuscularly and by intratracheal instillation (Langard, 1988). Inhalation exposure of animals to Cr(VI) compounds, however, has not reliably led to the occurrence of pulmonary tumors (Langard, 1990); only one positive study has been published (Nettesheim et al., 1971). Cr(VI) compounds have not been shown to be carcinogenic on ingestion.

Relatively soluble chromium compounds may briefly generate higher concentrations of available chromium in the lung than relatively insoluble compounds, but they are also more rapidly cleared. Evidence from experimental animal studies and from epidemiological studies of workers in chromium-related industries supports the hypothesis that the moderately-soluble chromate salts (Zn, Ca, Sr chromates) are the most potent respiratory carcinogens, while the highly soluble salts (Na, K, NH_4 chromates) are much less active (Hathaway, 1989; Gibb and Chen, 1989). Presumably, the less-soluble salts serve as persistent sources of low concentrations of locally available chromium (Gad, 1989).

2. Local Toxicity

Cr(VI) compounds are corrosive due their acidity and their oxidizing potential. Dermal contact results in irritation which can be sufficiently severe to lead to ulceration with consequent systemic uptake of the chromium. Ulceration or perforation of the nasal septum was formerly common in industries using chromates but is only rarely seen today. Dermal contact can also cause delayed sensitization and allergic dermatitis. These local actions of chromium are industrial problems. They do not occur in the general population.

Oral exposure to Cr(VI) compounds, like dermal exposure, may involve

irritation and corrosive action.

3. Systemic Toxicity

Apart from their carcinogenicity in the lung and any localized toxic actions, Cr(VI) compounds can be nephrotoxic in animals and in humans.

Acute exposure to Cr(VI) compounds leads to acute nephrotoxicity, which may be sufficiently severe to cause renal failure and death. In rats, the critical effect is an increase in urinary protein excretion (Gumbleton and Nicholls, 1988). Both tubular and glomerular damage occur (Appenroth and Bräunlich, 1988). Humans can also suffer renal tubular necrosis following massive Cr(VI) exposure (Goyer, 1990). Acute Cr(VI) exposure is treated by administration of ascorbic acid to reduce Cr(VI) to Cr(III) in the blood (Korallus et al., 1984).

Chronic kidney damage resulting from lower-level exposure of workers to Cr(VI) compounds has not been satisfactorily demonstrated. Elevated urinary ß-2-microglobulin (Lindberg and Vesterberg, 1983), retinol-binding protein (Franchini and Mutti, 1988), ß-glucuronidase (Mutti et al., 1979), and kidney brush border antigens (Franchini and Mutti, 1988) have been reported but are not consistently found (Verschoor et al., 1988). It has not been possible to define dose-response relationships for any of these effects (Franchini and Mutti, 1988). Based on what is known at the present time, it appears that the renal effects of chromium may be transient even during long-term exposure. There appears to be a threshold for renal tubular damage (Franchini and Mutti, 1988), which would be consistent with the hypothesis that Cr(VI) is systemically toxic only when the capacities of the multiple systems for its detoxification by reduction to Cr(III) have been exceeded.

Chronic animal studies have not been especially revealing with respect to the systemic toxicity of chromium. MacKenzie et al. (1958) observed only reduced water intake at the highest concentration, 25 mg/L, of Cr(VI) in rats given Cr(III) or Cr(VI) in the drinking water for one year. There were no effects on weight, food consumption, appearance or blood chemistry in any other experimental group.

C. MECHANISM OF CARCINOGENIC ACTION

Cr(VI) compounds are generally positive in short-term tests for mutagenicity in cellular systems (DeFlora et al., 1990). Bioavailability of Cr(VI) to the intact cells is an important factor determining mutagenic activity. Poorly-soluble compounds are not consistently positive in these test systems. Solubilization often enhances mutagenicity or, in the case of very poorly soluble chromium compounds, may be required for demonstration of genotoxicity. In acellular test systems, on the other hand, Cr(VI) compounds are not ordinarily genotoxic. Cr(III), in contrast, induces a wide range of genetic effects in acellular and subcellular systems but is generally inactive in bacterial and mammalian cell test systems (DeFlora et al., 1990). The contrasting activities of Cr(III) and Cr(VI) in cellular and acellular test systems are attributed to the selective permeability of cell membranes to Cr(VI) (Levis et al, 1978). Once in the cytoplasm, Cr(VI) is rapidly reduced to Cr(III), which cannot readily penetrate membranes (Grogan, 1958; Mertz, 1969).

Cr(III), but not Cr(VI), induces DNA-protein cross-linking in solution and in isolated nuclei (Fornace et al., 1981). In addition, Cr(VI) does not react with isolated DNA until it has been reduced to Cr(III) (Tsapakos and Wetterhahn, 1983). DNA single-strand breakage and DNA-protein cross-linkage have been observed both in vivo in rats given dichromate (Tsapakos et al., 1981) and in vitro in cultured mammalian cells incubated with soluble chromium salts (Fornace et al., 1981). The in vitro genotoxic effects are proportional to the concentration of chromate in the medium (Fornace et al., 1981); Sugiyama et al., 1986), and the in vivo effects are proportional to the chromate dose (Fornace et al., 1981).

On the basis of these observations, it was initially suggested that the genotoxic effects of chromium were due to actions of Cr(III) produced intracellularly from Cr(VI) (Tamino et al., 1981). However, Cr(III) binds to isolated native and synthetic DNA only at low levels compared with the amount of chromium bound when Cr(VI) is incubated with isolated DNA in the presence of a microsomal reducing system (Tsapakos and Wetterhahn, 1983). Therefore, attention has been directed at identification of electrophilic intermediates produced in the course of Cr(VI) reduction to Cr(III).

Cr(VI) is reduced intracellularly by a wide variety of enzyme systems: microsomal (Garcia and Wetterhahn Jennette, 1981; Alexander et al., 1986), mitochondrial (Rossi and Wetterhahn, 1989), and cytosolic (DeFlora et al., 1985; Banks and Cooke, 1986). It also is reduced nonenzymatically by electron donors such as thiols, especially glutathione (Connett and Wetterhahn, 1985; DeBetto et al., 1988), and by ascorbate (Connett and Wetterhahn, 1985; Suzuki, 1988). These reduction pathways are capable of producing a number of reactive intermediates. Cr(V) is produced during reduction of Cr(VI) by a cytochrome P-450-linked one-electron reduction (Wetterhahn Jennette, 1982), by electron transport chain complexes of the mitochondria (Rossi and Wetterhahn, 1989), by hydrogen peroxide (Kawanishi et al., 1986), by ascorbate (Goodgame and Joy, 1987), and by glutathione (Kawanishi et al., 1986; Goodgame and Joy, 1986). Cr(IV) is a possible intermediate in the reduction catalyzed by glutathione (Cupo and Wetterhahn, 1985; Shi and Dalal, 1989). Hydroxyl radicals and singlet oxygen are produced by the reaction of Cr(VI) with hydrogen peroxide (Kawanishi et al., 1986). Thioyl radicals may also be formed (Wetterhahn and Hamilton, 1989). Chromium reductive processes have been reviewed by Wetterhahn and Hamilton (1989). Because of the delicate balance among competing pathways of Cr(VI) reduction, the process may either activate or detoxify chromium (Bianchi and Levis, 1988) and the dependence of the carcinogenic action of Cr(VI) compounds on factors such as solubility and oxidation state is complex (DeFlora et al., 1989; Hathaway, 1989).

Recently, Wetterhahn has presented evidence suggesting that Cr(VI)-induced DNA lesions lead to alterations in gene expression (Wetterhahn and Hamilton, 1989).

D. KINETICS IN RATS

The following kinetic data are all for the rat unless otherwise noted.

1. Absorption

Oral. Cr(III) and Cr(VI) are absorbed to different extents from soluble salts in the gastrointestinal tract of rats. By comparison of concentrations of Cr^{51} in the blood 4-10 days after intravenous or oral administration of hexaaquo $CrCl_3$, Mertz et al. (1964) judged that 2-3% of the oral dose had been absorbed. The fraction absorbed was independent of dose (0.15 - 10.0 μg chromium/100 g) and of previous dietary chromium.

MacKenzie et al. (1959) monitored radiolabel in blood, tissues, urine, and feces of adult rats given single doses of Cr(VI) as Na_2CrO_4 by stomach tube. The amount of chromium excreted in the urine by day 14 was greater (6%) when the rats had been fasted prior to chromium administration than when they had not (3%). Comparison of average levels of radiolabel in blood, erythrocytes, and plasma after administration of Cr(VI) or Cr(III) demonstrated that Cr(III) was absorbed only 1/10 or less as well as Cr(VI), and was absorbed less efficiently in nonfasted than in fasted rats.

Pulmonary. Uptake and clearance of chromium from the lung are determined by many factors. Edel and Sabbioni (1985) demonstrated that chromium is much more efficiently absorbed in rat lung from a soluble Cr(VI) salt than from a soluble Cr(III) salt. Within a series of Cr(VI) salts of differing solubilities, systemic availability tends to parallel solubility (Bragt and van Dura, 1983). The range of half-lives reported for clearance of chromium from the lung (Bragt and van Dura, 1983); Weber, 1983) suggests that chromium is present in the lung in different states or compartments from which it is cleared at different rates. Particle size distribution of the chromium-containing aerosol is also a critical factor, since it will determine localization of the chromium within the lung. Unfortunately, little is known about most of these factors as they relate either to individual chromium compounds or to the mixture of salts that may be present in the lung after administration of a single chromium-containing compound. There is insufficient information to model the lung as anything other than a single tissue with competing losses due to absorption of chromium into the systemic circulation and to its transfer to the gastrointestinal tract via the mucociliary escalator.

That the lung-to-gastrointestinal tract transfer is important was shown by Langård et al. (1978), who observed rapid increases in fecal chromium during 6-hour inhalation exposures of rats to dusts of $ZnCrO_4$, a moderately soluble Cr(VI) salt. Bragt and van Dura (1983) showed that the amount of chromium appearing in the feces increased sharply as the solubility of the Cr(VI) salt decreased, with as much as 80% of an intratracheal dose of insoluble $PbCrO_4$ accumulating in feces by the ninth day post-administration compared with 20% of an intratracheal dose of soluble Na_2CrO_4. The figure of 20% for Na_2CrO_4 was confirmed by Weber (1983) and by Edel and Sabbioni (1985), who showed also that 36% of the soluble Cr(III) salt $CrCl_3$ was excreted in the feces by the seventh day after a single intratracheal administration, presumably because the Cr(III) was less efficiently cleared by systemic absorption.

At least some of the Cr(VI) reaching the systemic circulation from the lung persists as Cr(VI) until it reaches red cells. When a Cr(III) salt and a Cr(VI) salt were given intratracheally and the distribution of chromium between plasma and red cells measured 24 hours later (Edel and Sabbioni, 1985), 15% of the blood chromium was found in the red cells after Cr(III) administration but 61% in the red cells after Cr(VI) administration. Thus, a significant fraction of the

absorbed Cr(VI) had become associated with the red cells as Cr(VI) before it could be reduced to Cr(III).

The kinetics of clearance of chromium salts from the lung suggest that systemic absorption is largely a rapid process that may be complete within an hour after a single intratracheal dose (Bragt and van Dura, 1983). Subsequent clearance of chromium from the lung can be described as a sum of exponential terms with half-lives of the order of days up to a month (Bragt and van Dura, 1983; Weber, 1983). Pulmonary clearance of chromium is not dose-dependent within a reasonable dose range (Bragt and van Dura, 1983; Weber, 1983).

2. Distribution

Hopkins (1965) and Mertz et al. (1964) studied the distribution of Cr(III) chloride administered intravenously as $Cr^{51}Cl_3$. Hopkins monitored adult and weanling rats for up to 4 days following chromium administration. He found that the spleen and kidney continued to accumulate chromium over the 4-day observation period and that the liver, testis and epididymis also lost chromium slowly. Slow loss of chromium from liver, kidney, and spleen has consistently been noted (MacKenzie et al., 1959; Bragt and van Dura, 1983; Edel and Sabbioni, 1985). A relatively large fraction of chromium is also taken up by the bone marrow in rabbits (Kraintz and Talmage, 1952) and rats (Bragt and van Dura, 1983). This general distribution gave rise to the early suggestion that chromium is trapped by the reticuloendothelial system (Kraintz and Talmage, 1952). Whatever the mechanism for the delay, it is clear that kidney, spleen, and bone marrow, and to a less marked degree liver, are cleared of their chromium more slowly than are other tissues.

Cr(III) is transported in association with proteins, mostly globulins, in blood plasma. Unless Cr(III) is present in excess, the majority of it travels with the iron-binding protein siderophilin (Hopkins and Schwartz, 1964). A fraction of the Cr(III) in plasma is complexed with low-molecular-weight ligands (Mertz, 1969), and it is this small fraction that may be able to traverse membranes and thus diffuse out of the blood. It is also possible that small, stable coordination complexes of Cr(III) may traverse membranes by endocytosis (Bianchi and Levis, 1988), although no direct evidence for such a mechanism has been presented. In the cytoplasm also, chromium appears to be associated with both high-molecular-weight and low-molecular-weight complexes (Yamamoto et al., 1981; Edel and Sabbioni, 1985).

No dose- or sex-dependence of chromium distribution in rats at intravenous doses between .01 μg/100 g and .1 μg/100 g has been observed (Hopkins, 1964; Mertz et al., 1964). Previous dietary history, including feeding of a chromium-deficient Torula yeast diet, does not affect distribution or kinetics (Hopkins, 1964; Mertz et al., 1964). Compartmental analysis yielded a 3-term expression for the body burden of Cr51 with half-lives of 0.5 days, 5.9 days, and 83.4 days (Mertz et al., 1964).

Witmer (1991) reported that bone is a significant repository for chromium after oral or intraperitoneal administration of chromate salts to rats. Weber (1983) had found that after administration of a radiolabelled chromate salt by intratracheal intubation, the radioactivity was found to be located primarily in the epiphyseal region of the long bones. The distribution of radiolabel was reported to be similar to that seen after administration of bone-seeking tracers

like Ca^{45} or Sr^{89}. Kraintz and Talmage (1952) had also noted localization of radiolabel in the epiphyses of long bones after intravenous administration of $Cr^{51}Cl_3$ to rabbits.

Hopkins (1965) observed that the bone of young, growing rats tended to concentrate chromium with time (7% increasing to 12% of the dose) after an intravenous injection of $Cr^{51}Cl_3$, while the bone of mature rats acquired less label initially (4% of the dose) and the amount of chromium in mature bone did not increase with time. These observations strongly suggest that incorporation of chromium into bone is associated with growth of new bone. It may be inferred that rapid surface exchange of blood and bone chromium accounted for around 4% of the dose while the additional incorporation of chromium into bone of growing rats was due to bone growth.

3. Excretion

Renal. The percentage of a chromium dose that is excreted in the urine is not dependent on the oxidation state of the administered chromium. About 21-22% is excreted in the 24 hours following an intravenous dose of a soluble salt of either Cr(III) or Cr(VI) in rats (Cikrt and Bencko, 1979).

Biliary. Not all chromium is excreted in the urine. Cikrt and Bencko (1979) found that .5% of an intravenous dose of $Cr^{51}Cl_3$ and 3.5% of an intravenous dose of $Na_2Cr^{51}O_4$ were excreted in the bile of rats in 24 hours. The principal difference was a more rapid excretion of Cr(VI) during the first few hours after administration. Cavalleri et al. (1985) administered $K_2Cr^{51}O_4$ to adult rats to determine total chromium and Cr(VI) appearing in bile. They found that about 2% of the dose was excreted in the bile within 2 hours; less than 1% of this amount was excreted as Cr(VI). These percentages were independent of dose from 0.1-1 mg chromium. Cr(VI) was found to be stable in bile. Thus, while most of an intravenous Cr(VI) dose is reduced to Cr(III) before its excretion, a small fraction appears in the bile as Cr(VI). The authors speculated that the mechanism of excretion might be diffusion through intercellular spaces without entry into the hepatocyte where reduction would presumably have occurred. Such a mechanism could also account for part of the excretion of Cr(III) in the bile.

Interestingly, Cikrt and Bencko (1979) found that the gastrointestinal tract contents and feces together accounted for 4.2% of an intravenous Cr(III) dose and 7.3% of an intravenous Cr(VI) dose in rats after 24 hours, suggesting a fairly substantial gastrointestinal excretion. If the gastrointestinal and biliary excretion data from Cikrt and Bencko are combined with urinary excretion from MacKenzie et al. (1959) to estimate the fractional absorption from the gastrointestinal tract, the calculation would suggest (6+7.3+3.5)=17% absorption of Cr(VI) by fasted rats and 13.8% by fed rats, and about 7% or possibly a little less of Cr(III) by fasted rats. Even these figures are minima, since biliary and fecal excretion were evaluated by Cikrt and Bencko only to 24 hours post-administration.

4. Reduction of Cr(VI) to Cr(III)

Enzymatic and nonenzymatic reduction of Cr(VI) to Cr(III) occurs in virtually all tissues and body fluids, including saliva, gastric juice, and alveolar fluids (Petrilli and DeFlora, 1988). Cavalleri et al. (1985) reported that no appreciable reduction of Cr(VI) occurs in rat bile. In rat whole blood

and plasma *in vivo*, the half-life of intravenous Cr(VI) is less than a minute (Cavalleri et al., 1985).

II. DEVELOPMENT OF A PHYSIOLOGICALLY-BASED MODEL OF CHROMIUM KINETICS IN THE RAT

A. Transformation of Data for Modeling Application

The blood, blood plasma, red cell, and urine chromium analyses carried out by inductively coupled plasma emission spectroscopy were plagued by the high salt content of the samples. Therefore, the theoretical reduction in detection limit made possible by use of this analytical method was to some extent offset by increased uncertainty of measurement at these low sample chromium contents. Values of the reagent blanks that accompanied the runs are not shown in the raw data printout. For entry into the chromium kinetic model, these data were adjusted by subtraction of the reagent blanks for each analytical run as well as by subtraction of background (control) values.

Reagent blanks for some of the runs were substantially higher than the recorded sample values for the run. This occurred with three groups of blood samples: inhalation control, inhalation Cr(III), and inhalation Cr(VI). Since other tissues from the inhalation control group contained essentially no chromium, blood concentrations in this group were set to zero. Blood chromium in the other two high-blank groups were adjusted by subtraction of an arbitrary blank value, but were considered unreliable and were given no weight in modeling the inhalation data.

The data as they were used for model development are given in Table 1.

B. Qualitative Overview of Data

Soluble Cr(III) was barely absorbed from the GI tract in the group given Cr(III) in the drinking water. While traces of chromium were found in blood and urine, the range of values overlapped almost completely the range of values seen in controls, and bore no systematic relationship to the length of exposure. Traces of chromium found in the liver in this experimental group were essentially equivalent to amounts in controls. Kidney, muscle, and lung were negative for chromium.

Soluble Cr(VI) was absorbed from the drinking water to a slight extent. Chromium was elevated by Day 2 of exposure in blood, liver, and kidney, and increased steadily and in proportion to the length of exposure in all three tissues. By Day 20 of exposure, lung and muscle also were positive for chromium. The rate of excretion of chromium in urine was in direct proportion to its concentration in the well-perfused tissues, liver and kidney, as well as to its concentration in blood.

These experimental observations on gastrointestinal uptake of chromium are entirely consistent with the reported absorption by rats of 3% of a single oral dose of Cr(VI), Cr(III) being absorbed only 1/10 or less as well (MacKenzie et al. (1959).

Fecal chromium was high, as expected, in all rats given chromium in the drinking water. However, it was not as high as predicted by the model on the basis of mass balance considerations. One possible explanation for the discrepancy is that the rate of excretion of feces may have been lower during the time the rats were in the metabolism cages than it would normally have been.

Intestinal chromium also was high in the rats given chromium in the drinking water. Chromium measured in the intestine was probably due to contamination by chromium from intestinal contents, since it was too high to be explicable even as direct absorption from the GI tract and since it was very erratic. Intestinal and fecal chromium measurements were not used in setting parameter values in the model.

Soluble Cr(III) was essentially not absorbed from the lung. Liver and kidney had no measurable chromium, while the lung accumulated about three times the amount of chromium that accumulated during inhalation exposure to Cr(VI). Soluble Cr(VI) was absorbed to a limited extent from the lung, with liver and kidney having small amounts of chromium that increased with the length of exposure. Fecal chromium was very slightly higher at most time points in the Cr(III) inhalation group than in the Cr(VI) inhalation group, reflecting clearance of the larger amounts of chromium retained in the lung during Cr(III) inhalation. Again, what appeared as intestinal chromium could best be explained as contamination by chromium from the gastrointestinal tract.

The experimental observations in the inhalation groups, like those in the oral chromium groups, are qualitatively consistent with the expected picture of limited absorption of Cr(VI) and minimal absorption of Cr(III), initial distribution into well-perfused tissues like liver and kidney, and slower appearance in poorly perfused tissues like muscle. Fitting of the chromium concentration data by a kinetic model, as discussed in the next section, yields additional information about clearances as well as quantitative estimates of parameter values.

C. General Model Outline

The basis of the model is a general model of rat body and bone growth from birth to maturity (O'Flaherty, 1991a). The chromium model consists of liver, kidney, gastrointestinal tract, lung, bone, other well-perfused tissues, and other poorly-perfused tissues. Erythrocytes and plasma are also modeled separately for Cr(VI). In adapting the general model to describe lead kinetics (O'Flaherty, 1991b), it was assumed that plasma lead exchanges rapidly with calcium at bone surfaces and slowly with calcium throughout the total bone volume, and in addition that lead is incorporated together with calcium into forming bone and returned to the plasma when existing bone is resorbed. In accordance with the observations of Hopkins (1965), discussed above, on localization and rates of uptake of chromium in bone of juvenile and mature rats, mechanisms of chromium uptake into bone are here considered to be rapid surface exchange with calcium and incorporation into forming bone. There is no evidence for a slow heterionic exchange of chromium with calcium in bulk bone. Chromium in the model is returned to blood rapidly from bone surfaces, and more slowly as bone is resorbed.

Exchange of Cr(VI) between blood and tissues other than bone is assumed to be flow-limited; that is, to be more rapid than the rate of blood flow through the tissue. Partition coefficients are not used for Cr(VI). It is assumed that Cr(VI) is not selectively bound in tissues in quantities sufficiently great to have an impact on overall kinetic behavior (see Discussion).

Exchange of Cr(III) between blood and tissues other than bone is assumed to be so slow that it can be described as diffusion-limited. Clearances must

therefore be assigned to these processes, and to whole-body Cr(III) loss, that are smaller than blood flow rates.

Reduction of Cr(VI) to Cr(III) is assumed to take place in all tissues with the exception of bone, as well as in the gastrointestinal tract. Reduction in tissues is modeled as a first-order process with a single rate constant whose magnitude is independent of the tissue in which reduction is taking place. In view of the complexity and variety of enzyme-mediated and enzyme-independent mechanisms contributing to chromium reduction, there is no theoretical basis for attempting a more precise description of the reduction process than this "average" approach.

No attempt is made to include binding of chromium to plasma or tissue proteins. Such binding has been neither qualitatively nor quantitatively characterized, and there is no evidence to suggest that it is rate-limiting in general. Slower return of chromium from the kidney than from other well-perfused tissues is handled by assigning a smaller clearance value to the kidney.

Excretion of both Cr(III) and Cr(VI) from the body is modeled as first-order loss from the kidney (into urine), from the liver (into bile), and from the intestine (into the gastrointestinal tract). Reabsorption of chromium from the intestinal contents (enterohepatic circulation) is included in the model.

Absorption of chromium from the gastrointestinal tract is modeled directly into the liver. Absorption from the lung is modeled directly into arterial blood. Absorption from the lung, the rate of which is compound-specific, competes in the model with mucociliary clearance from the lung to the gastrointestinal tract, a process whose rate is not compound-specific. Chromium entering the gastrointestinal tract from the lung is subject to reduction and/or absorption, as appropriate to its oxidation state.

D. Model Development

A flow chart of the process of development of this model is given as Appendix A. At each step in the flow chart, an additional degree of complexity was introduced, initial values of the new parameters were estimated based on literature data or data from the current study, and the predictions of the model were visually optimized to published data or to the current data set, as appropriate. The separate steps are described in greater detail in this section.

The general structure of the Cr(III) model was taken from an existing model of Pb kinetics. Parameters related to body growth and growth of bone, other tissues and organs, and all general physiological parameters have previously been defined and assigned values (O'Flaherty, 1991 a,b). One-half percent of the total bone volume is designated the compartment of rapid surface exchange. While the overall behavior of the model is insensitive to the size of this compartment below about 1% of total bone volume, the assigned compartment size gives an amount of bone chromium uptake in mature rats that is comparable to that reported by Hopkins (1965).

An initial value for whole-body Cr(III) clearance was estimated from the second term of the three-term sum-of-exponential fit to the chromium body burden data of Mertz et al. (1964) as follows:

$t1/2=5.9$ da

Clearance volume = 0.8*Body weight

For a 250-g rat,

Clearance =.250 L*0.8/5.9 da

=.034 L/da

Scaling in accordance with the .75 power of body weight, whole-body clearance of Cr(III) would be .096 L/da/kg. This figure was used as the initial value of the clearance of Cr(III) from the plasma. This parameter value and the value of fractional uptake of chromium from blood into forming bone were set by visually optimizing the model to Mertz' data for whole-body loss of Cr(III) from a single intravenous injection. The value of the bone uptake parameter, 50L blood cleared of chromium/L of new bone formed, is 0.33% of the corresponding value for lead. Clearance of Cr(III) from blood was optimized to 0.2 L/day, somewhat larger than the estimate of whole-body clearance that was used as an initial value since chromium is not evenly distributed throughout the body but is sequestered in the bone. Figure 1 compares the model simulation with the published line of best fit from Mertz et al. (1964).

Model predictions were compared to the data of Hopkins (1965) to obtain rough estimates of Cr(III) clearances between blood and soft tissues and of the rapid exchange of Cr(III) at bone surfaces. Table 2 presents the simulated and reported (by Hopkins, 1965) short-term uptake of Cr(III), given by intravenous injection, into bone of juvenile and mature rats. Values of the Cr(III) distribution parameters were adjusted by comparison of predicted with observed tissue concentrations at 4 and 42 days after a single intravenous dose (Visek et al., 1953). Because these tissue distribution data are so limited and because of concern that the behavior of Cr(III) salts injected intravenously may not be typical of the kinetic behavior of other chromium salts, the estimated values of distribution clearance were further adjusted throughout the model development process as suggested by fits of model predictions to other data sets.

The model was opened up to Cr(VI) at this stage by addition of a first-order reduction of Cr(VI) to Cr(III) in all tissues. The first-order rate constant for this reduction process was assigned an initial value of 250 da-1 based on the reduction in rat blood in vivo reported by Cavalleri et al. (1985). This value was adjusted downward, to 40 da-1, to bring Cr(VI) absorption and distribution into line with the observations of Cikrt and Bencko (1979) and Edel and Sabbioni (1985). Cr(VI) clearance was rather arbitrarily assigned the value 2 L/kg/da for these comparisons, based on the relative rates of absorption of Cr(III) and Cr(VI) (MacKenzie et al., 1959) and their relative rates of appearance in the bile (Cikrt and Bencko, 1979). This is a very soft number. It could well be considerably larger - or smaller - than the assigned value. However, model predictions are almost entirely unaffected by its value since the rate of reduction of Cr(VI) to Cr(III) is so much greater than its rate of excretion. Even with the smaller rate constant of 50 4a-1, reduction of Cr(VI) to Cr(III) is so rapid that it cannot be rate-determining at any point in the chromium kinetic model.

Total clearances of Cr(III) and Cr(VI) were fractionated into clearances into bile, urine, and GI tract in accordance with the data of Cikrt and Bencko (1979), Norseth et al. (1982), and Cavalleri et al. (1985). The observations of these researchers are not entirely in agreement. "Best guess" estimates of 1% excretion into bile, 80% of the remainder into urine, and 20% of the remainder across the GI tract for Cr(III) and 5% excretion into bile, 80% of the remainder into urine, and 20% of the remainder across the GI tract for Cr(VI) were based primarily on the work of Cikrt and Bencko (1979).

The next step was to add a red cell compartment in communication with arterial plasma. Only Cr(VI) is modelled as capable of entering the red cell. Once inside, Cr(VI) is reduced to Cr(III) as it would be in any other tissue. The half-life of association of chromium with the red cell is well established; it is about 18 days in the rat (Bishop and Surgenor, 1964), substantially less than the survival time of the cell. Clearance of chromium from the red cell to the plasma was set at 0.004 L/da, corresponding to a half-life of 18 days in a red cell volume of 3.2% of body weight. The first-order rate constant for uptake of Cr(VI) from the plasma into the red cell was estimated later (see below).

Expansion of the model to accommodate uptake from the GI tract was undertaken at this point. The first-order rate constants for absorption of Cr(III) and Cr(VI) from the GI tract were initially set numerically equal to the fraction of a single oral dose absorbed (MacKenzie et al., 1959; Cikrt and Bencko, 1979), on the simplifying assumption that a single dose passes by absorbing sites in the intestine within a day. They were adjusted in order to reconcile model predictions with the data of MacKenzie et al. (1959), and optimized by visually fitting model predictions to the data from the current study.

The model was run for a one-year simulated exposure of rats to various concentrations of chromium in the drinking water, and the predicted concentrations in liver, kidney, and bone were compared with the data of MacKenzie et al. (1958) from the comparable chronic study. Table 3 gives the predicted and observed chromium concentrations in these tissues after a year's exposure.

The final step was to expand the model to include absorption and elimination of chromium from the lung. Since Cr(III) is essentially unabsorbed from the lung, the rapid reduction of Cr(VI) to Cr(III) that takes place in the lung is adequate in itself to account for the observation that systemic absorption of Cr(VI) from the lung is virtually complete within an hour or two. Therefore, the lung was modeled as a single physiological compartment from which only Cr(VI) is systemically absorbed while both Cr(III) and Cr(VI) are cleared by mucociliary action into the GI tract. The first-order rate constants for absorption of Cr(III) and Cr(VI) from the lung were initially set at 0 and 40 da-1, respectively, based on the study of Weber (1983). The initial value of the first-order rate constant for transfer of chromium from the lung to the GI tract via the mucociliary escalator was .035 da-1, taken from the terminal slope, with roughly a 25-day half-life, of the post-exposure lung chromium data of Weber (1983). The values of these parameters were unchanged by the process of visual optimization by comparison of model predictions with the inhalation data from the current study.

Final parameter values are given in Table 4.

TABLE 1

Summary of Experimental Data as Used For Model Development:
Mean values, N=6

Day of Study	Lung µg/Cr	Liver µg Cr/g	Intest. µg Cr/g	Kidney µg Cr/g	Muscle µg Cr/g	Blood ng Cr/ml	Urine µg Cr/da	Feces mg Cr/da
			I. Rats Exposed to Cr (VI) by Inhalation					
2	1.95	nd	1.19	nd	nd	42.5	.520	nd
5	5.10	.060	1.12	.217	nd	58.4	.207	nd
10	7.53	.062	1.37	.237	nd	73.8	.266	.018
20	13.3	.066	2.36	.310	.047	72.8	.135	.048
40	24.3	.089	3.24	.580	.054	75.7	.047	.082
60	13.0	.038	.82	.137	.027	39.8	.012	nd
			II. Rats Exposed to Cr(VI) in Drinking Water					
2	nd	.209	15.5	.249	nd	9.0	.622	.997
5	nd	.372	22.7	.588	nd	11.8	1.79	.835
10	nd	.585	14.4	1.60	nd	18.5	2.01	.949
20	1.17	1.18	29.0	1.71	.077	48.9	3.08	.977
40	.65	1.50	6.8	1.90	.103	58.3	2.19	1.51
60	.45	.509	.83	.634	.070	11.3	.217	nd
			III. Rats Exposed to Cr(III) by Inhalation					
2	3.43	nd	3.57	nd	nd	61.5	.215	.028
5	8.43	nd	4.19	nd	nd	64.8	.101	.035
10	17.1	nd	25.6	nd	nd	23.4	.084	.016
20	35.4	nd	39.4	nd	nd	12.0	.032	.032
40	63.7	nd	4.80	nd	nd	105.7	.002	.074
60	42.9	nd	.84	nd	nd	89.0	.001	nd
			IV. Rats Exposed to Cr(III) in Drinking Water					
2	nd	.042	18.3	nd	nd	2.48	.227	.821
5	nd	trace	17.2	nd	nd	3.11	.065	.729
10	nd	.034	20.6	nd	nd	16.8	.040	1.20
20	nd	nd	26.8	nd	nd	5.60	.075	1.07
40	nd	nd	7.15	nd	nd	4.72	.017	1.12
60	nd	trace	.83	nd	nd	5.52	nd	nd

TABLE 1 (Continued)

Summary of Experimental Data as Used For Model Development:
Mean values, N=6

Day of Study	Lung µg/Cr	Liver µg Cr/g	Intest. µg Cr/g	Kidney µg Cr/g	Muscle µg Cr/g	Blood ng Cr/ml	Urine µg Cr/da	Feces mg Cr/da
			V. Control Rats (Inhalation Study)					
2	nd	.036	1.13	nd	nd	nd	.042	nd
5	nd	.041	.64	nd	nd	nd	.001	nd
10	nd	nd	.83	nd	nd	nd	nd	nd
20	nd	nd	1.08	nd	nd	nd	nd	.02
40	nd	.041	1.08	nd	nd	nd	nd	nd
60	nd	.032	.84	nd	nd	nd	nd	nd
			VI. Control Rats (Drinking Water Study)					
2	nd	nd	.65	1.58	trace	1.5	.017	nd
5	nd	nd	.83	nd	trace	1.6	nd	.002
10	nd	nd	.56	nd	nd	4.2	.003	nd
20	nd	nd	.85	nd	trace	3.4	nd	.013
40	nd	.035	.68	nd	trace	6.8	.010	nd
60	nd	.032	.72	nd	.038	2.5	nd	nd

TABLE 2

Fraction of a Single IV Dose of $Cr^{51}Cl_3$ Retained In Bone

	Time Post-Administration, hr					
	.25		4		24	
	Obs	Sim	Obs	Sim	Obs	Sim
Weanling Rats (1 month old)	.069	.067	.094	.027	.12	.015
Mature Rats (6 months old)	.043	.067	.053	.045	.047	.018

Date from Hopkins, 1965

TABLE 3

Concentrations of Chromium in Tissues of Rats Following a One-Year Chronic Exposure to Chromium in Drinking Water

Concentration in Drinking Water, mg/L	Concentrations in Tissue, μg/g					
	Liver		Kidney		Bone	
	Obs	Sim	Obs	Sim	Obs	Sim
4.5 (Cr(VI))	.31	.74	1.6	1.05	2.3	2.45
7.7 (Cr(VI))	.62	1.27	2.8	1.80	4.2	4.20
11.2 (Cr(VI))	1.4	1.84	4.2	2.62	5.0	6.11
25.0 (Cr(VI))	12.1	4.11	5.7	5.84	6.4	13.6
25.0 (Cr(VI))	1.9	.29	.44	.25	1.1	.61

Data from MacKenzie et al., 1958; male, female data averaged.

TABLE 4

Parameter Values

Parameter	Description	Value
QEC3	Total body clearance of Cr(III)	.2 L/kg/da
QEB3	Clearance from liver	.01*QEC3
QEU3	Clearance from kidney	.8*(QEC3-QEB3)
QEI3	Clearance from GI tract	.2*(QEC3-QEB3)
QEC6	Total body clearance of Cr(VI)	2 L/kg/da
QEB6	Clearance from liver	.05*QEC6
QEU6	Clearance from kidney	.8*(QEC6-QEB6)
QEI6	Clearance from GI tract	.2*(QEC6-QEB6)
WDINC	Diffusion constant, Cr(III) into well-perfused tissues	.3 L/kg/da
PDINC	Diffusion constant, Cr(III) into poorly-perfused tissues	.1 L/kg/da
BDINC	Diffusion constant, Cr(III) into bone	.15 L/kg/da
WDOUTC	Diffusion constant, Cr(III) out of well-perfused tissues	.012 L/kg/da
KDOUTC	Diffusion constant, Cr(III) out of kidney	.006 L/kg/da
PDOUTC	Diffusion constant, Cr(III) out of poorly-perfused tissues	.1 L/kg/da
BDOUTC	Diffusion constant, Cr(III) out of bone	.0005 L/kg/da
KIN6	First-order rate constant for Cr(VI) transfer into red cell	1/da
KOUT	First-order rate constant for loss of Cr from red cell	.00045/da
KRED	First-order rate constant for reduction of Cr(VI) to Cr(III)	40/da
KREDGI	First-order rate constant for reduction of Cr(VI) to Cr(III) in the GI tract	2/da
KMUCO	First-order rate constant for mucociliary clearance of Cr(III) and Cr(VI) from lung to GI tract	.035/da
KGI3	First-order rate constant for absorption of Cr(III) from GI tract	.002/da

TABLE 4 (Continued)

Parameter Values

Parameter	Description	Value
KGI6	First-order rate constant for absorption of Cr(VI) from GI tract	.1/da
KLU3	First-order rate constant for absorption of Cr(III) from lung	0/da
KLU6	First-order rate constant for absorption of Cr(VI) from lung	40/da
DEP3	Fractional deposition of Cr(III) in lung	.05
DEP6	Fractional deposition of Cr(VI) in lung	.05
CR	Fractional uptake of chromium from blood into forming bone	50 L blood/L bone

FIGURE 1

Printed line is simulation. Hand-drawn line is line of best fit from Mertz et al. (1965).

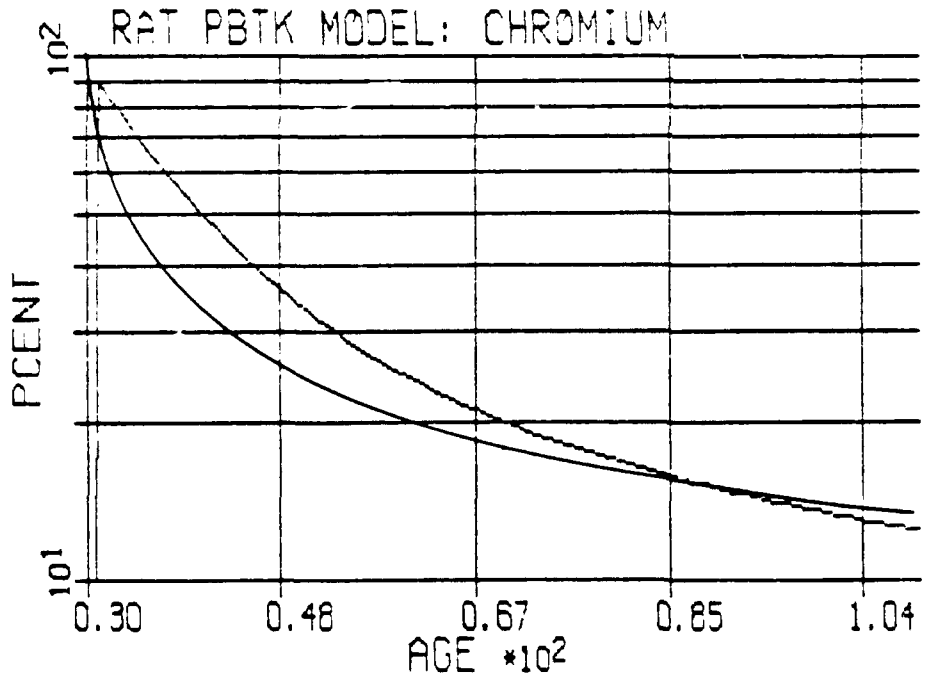


FIGURE 2

Liver chromium after single intratracheal administration of Cr(VI). Line is simulation. Data from Weber (1983).

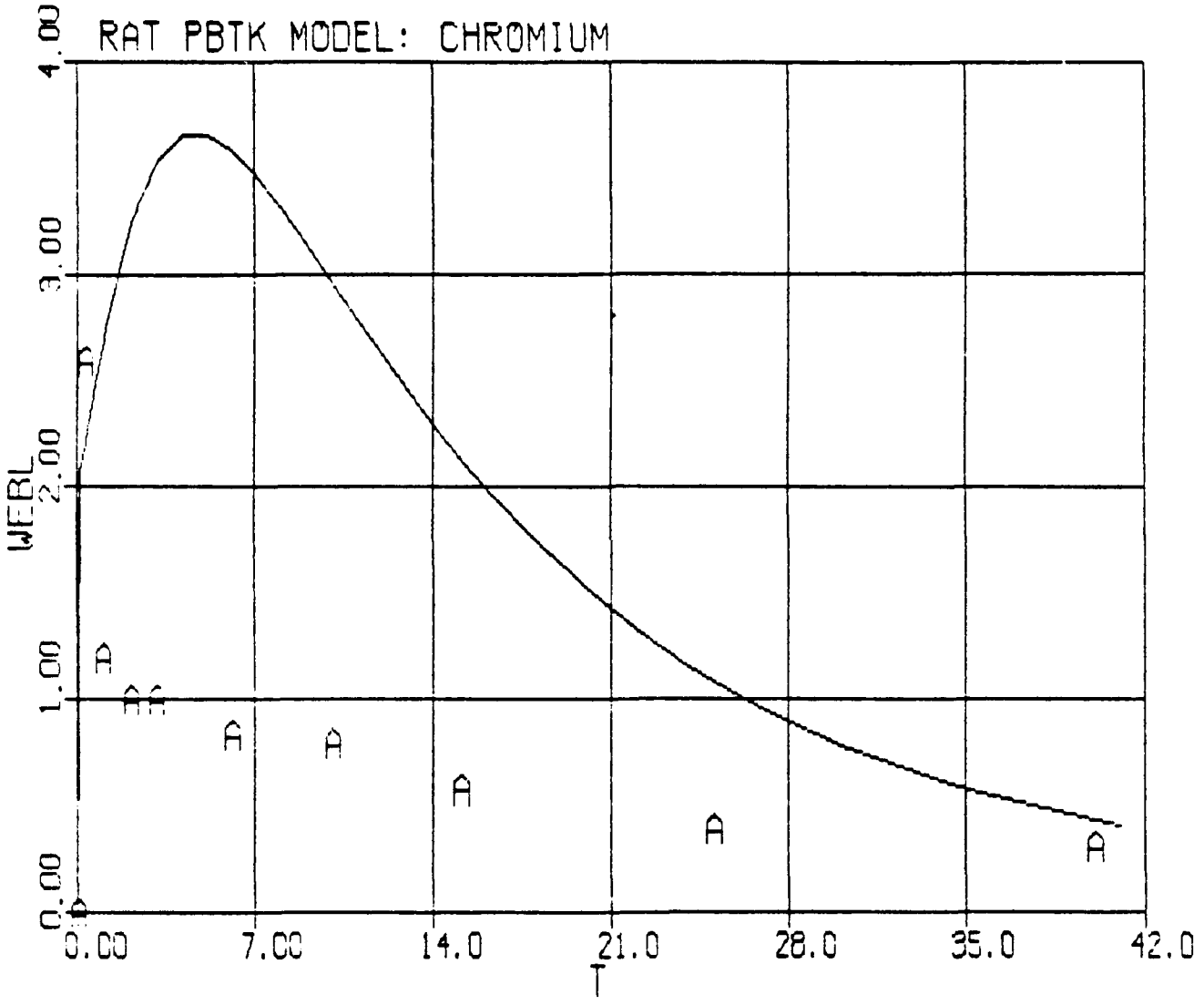


FIGURE 3

Lung chromium after single intratracheal administration of Cr(VI). Line is simulation. Data from Weber (1983).

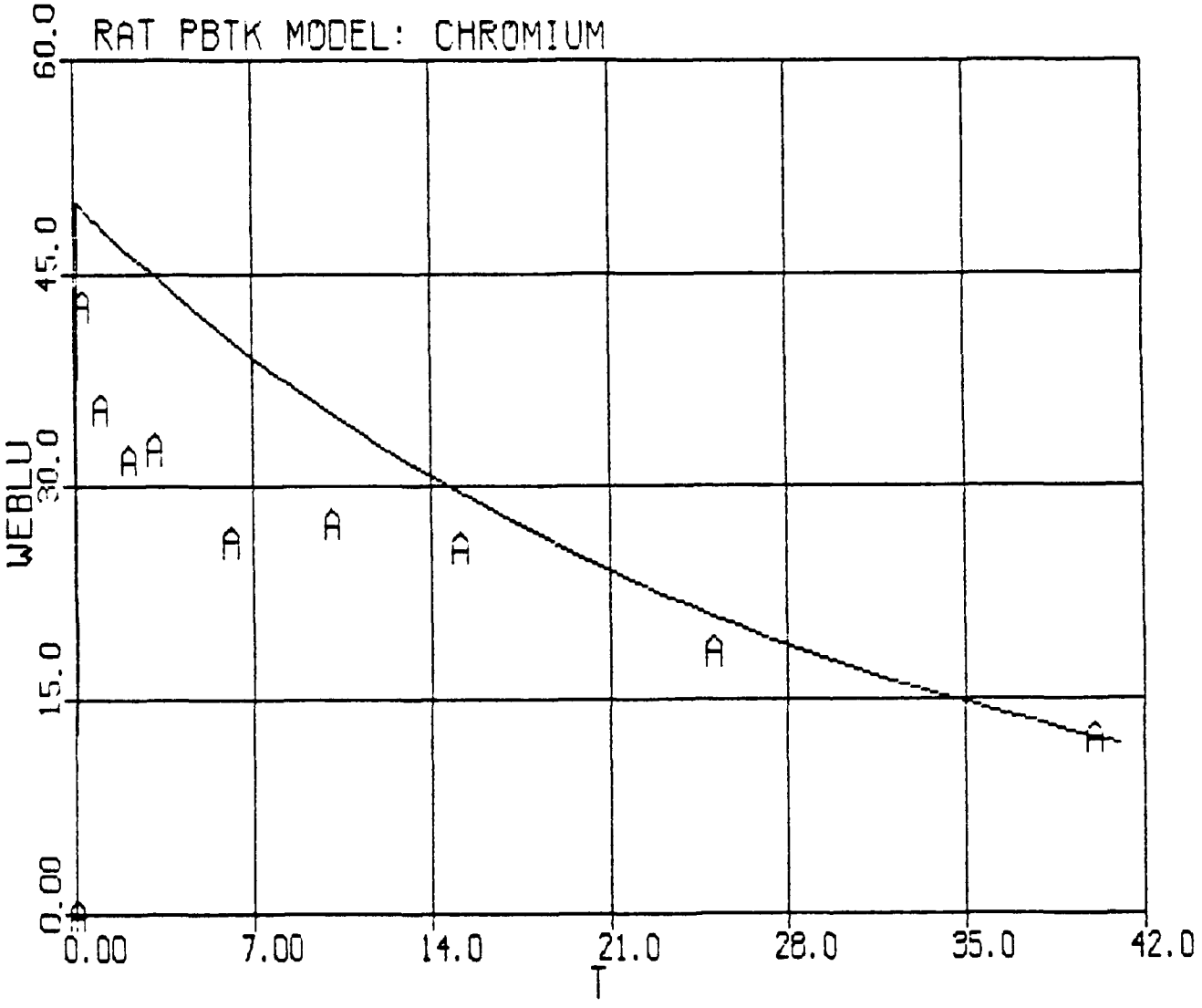


FIGURE 4

Kidney chromium after single intratracheal administration of Cr(VI). Line is simulation. Data from Weber (1983).

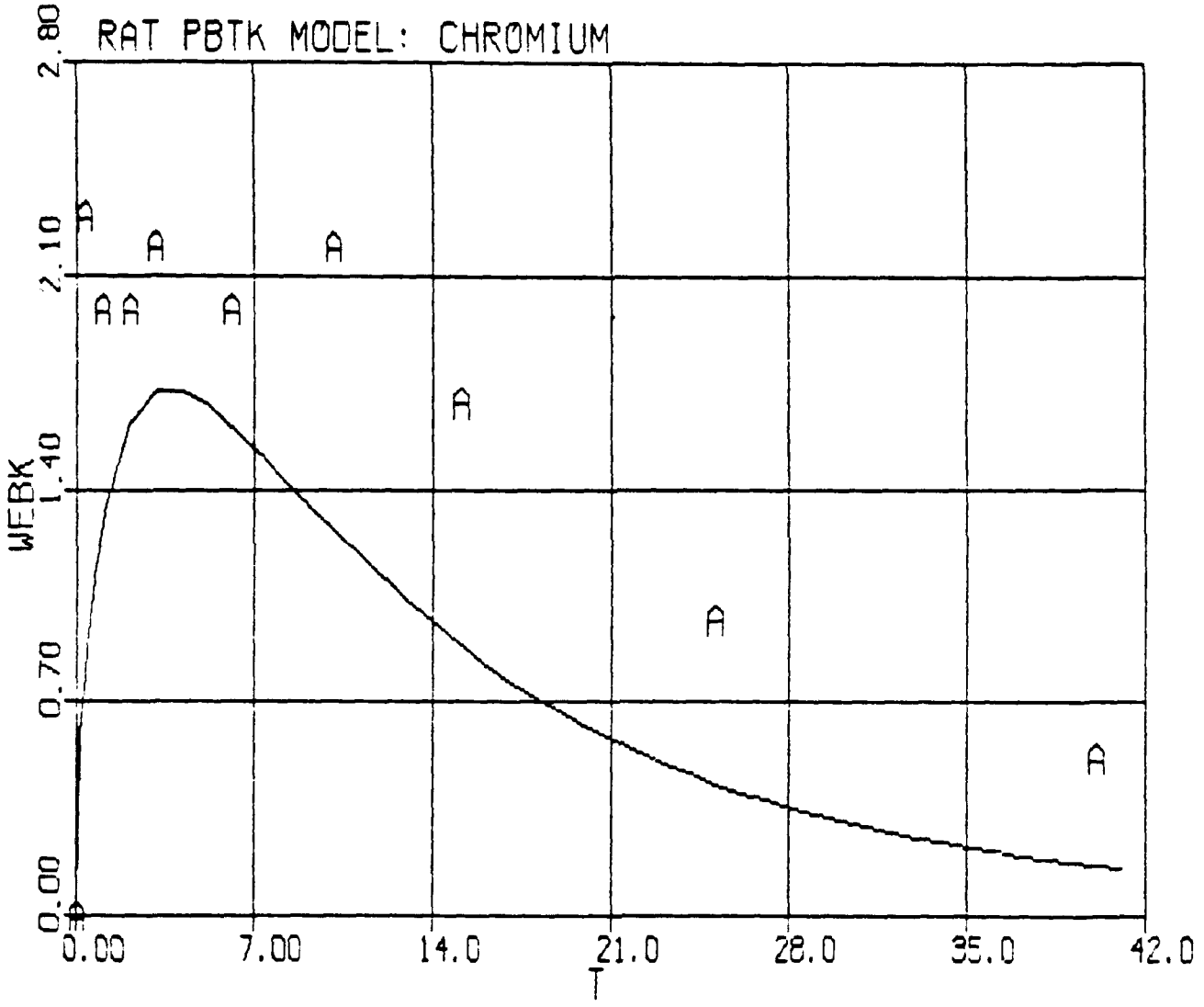


FIGURE 5

Intestinal tract chromium after single intratracheal administration of Cr(VI). Line is simulation. Data from Weber (1983).

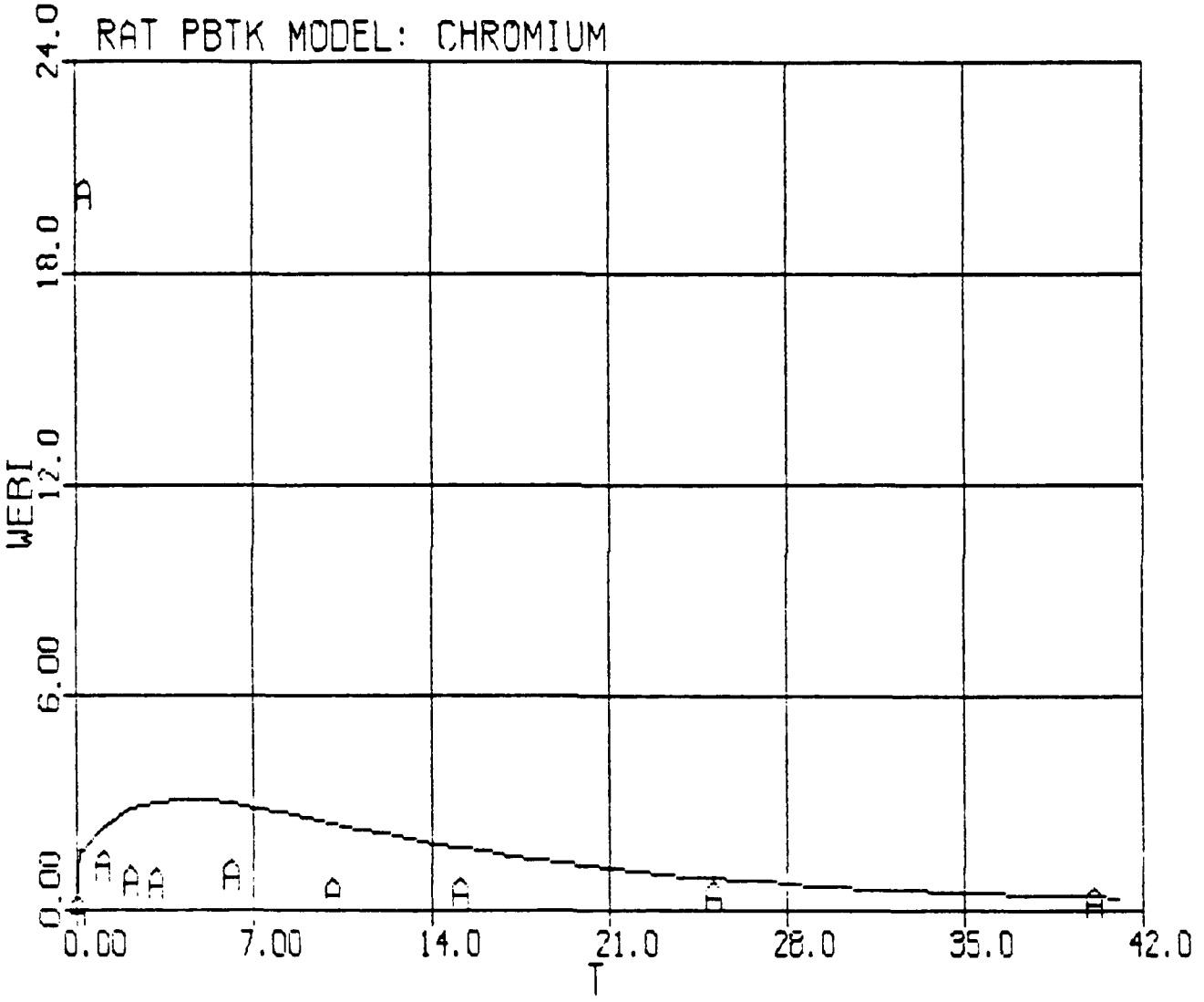


FIGURE 6

Body burden of chromium after single intratracheal administration of Cr(VI). Line is simulation. Data from Weber (1983).

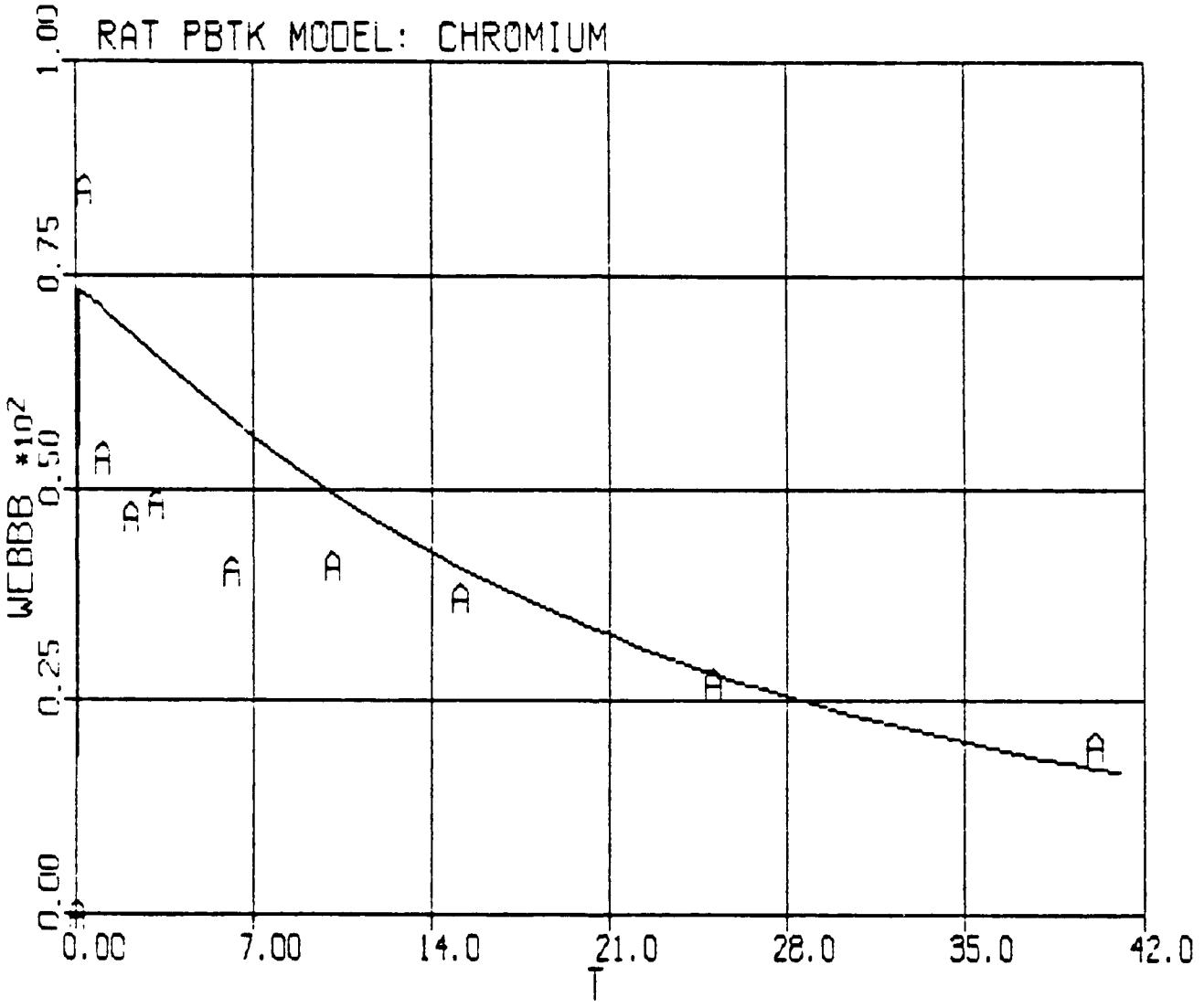


FIGURE 7

Chromium in blood during and after daily oral administration of Cr(III) (lower line) or Cr(VI) (upper line) for 40 days. Lines are simulations. Data from current study.

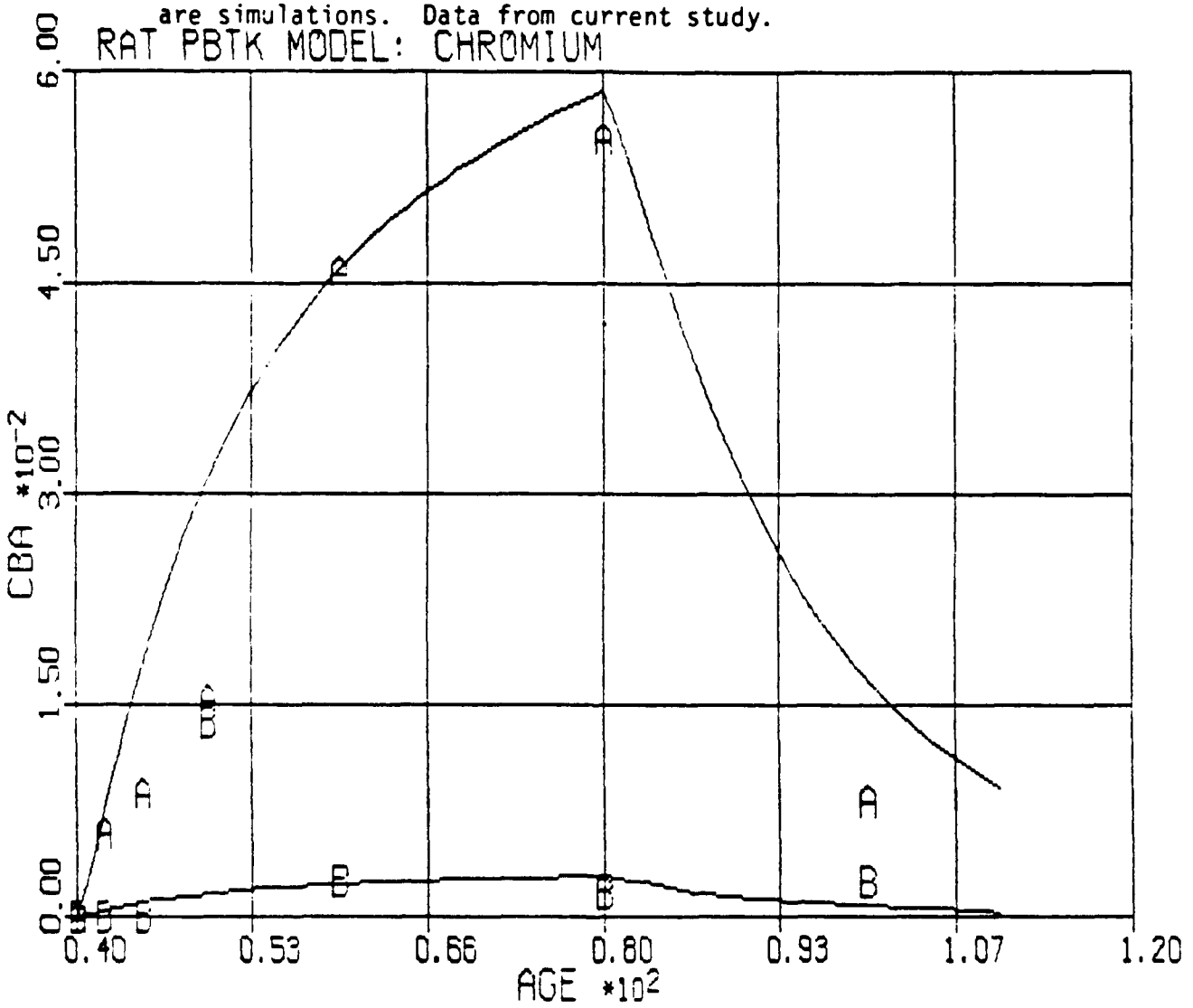


FIGURE 8

Chromium in liver during and after daily oral administration of Cr(III) (lower line) or Cr(VI) (upper line) for 40 days. Lines are simulations. Data from current study.

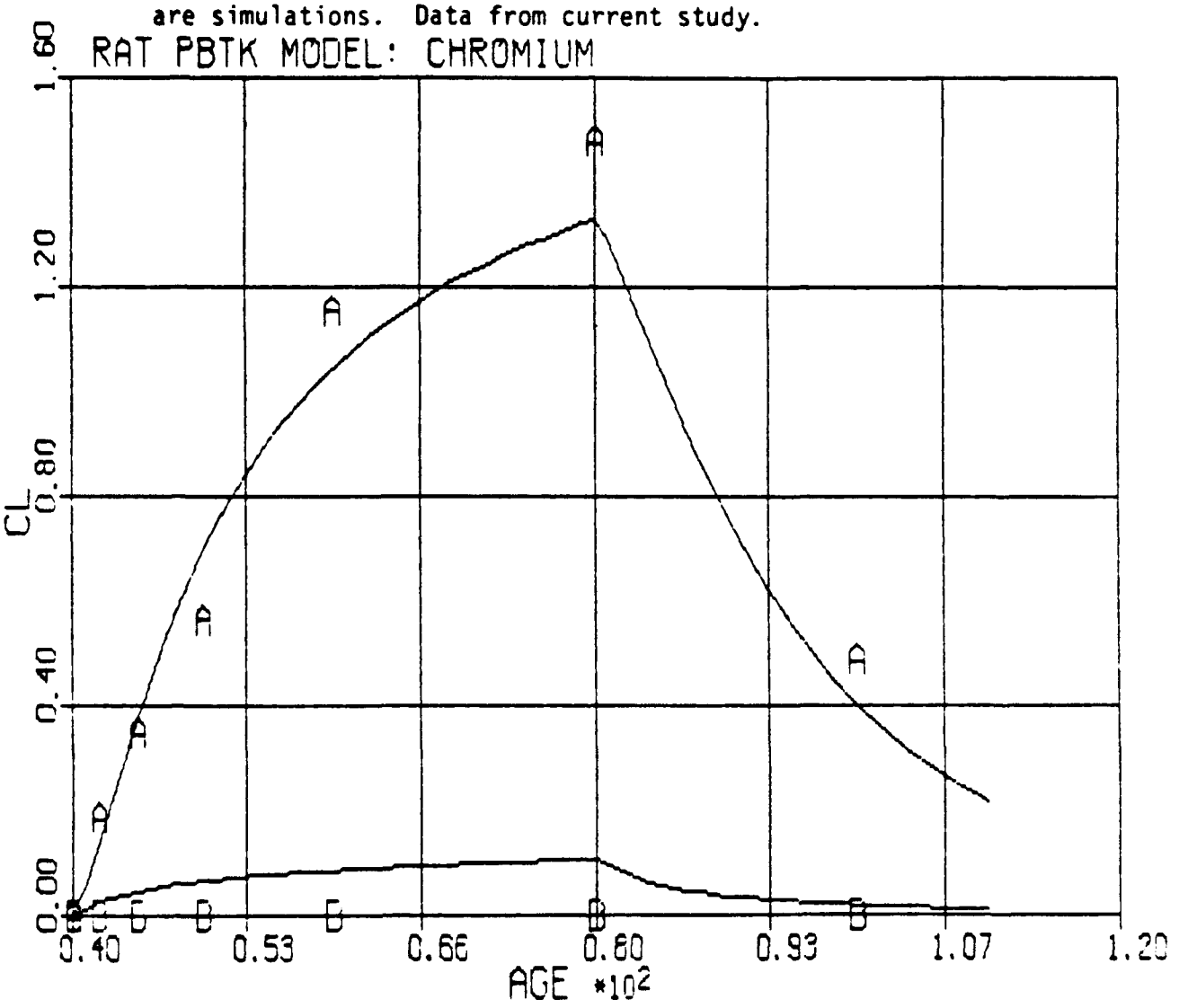


FIGURE 9

Chromium in kidney during and after daily oral administration of Cr(III) (lower line) or Cr(VI) (upper line) for 40 days. Lines are simulations. Data from current study.

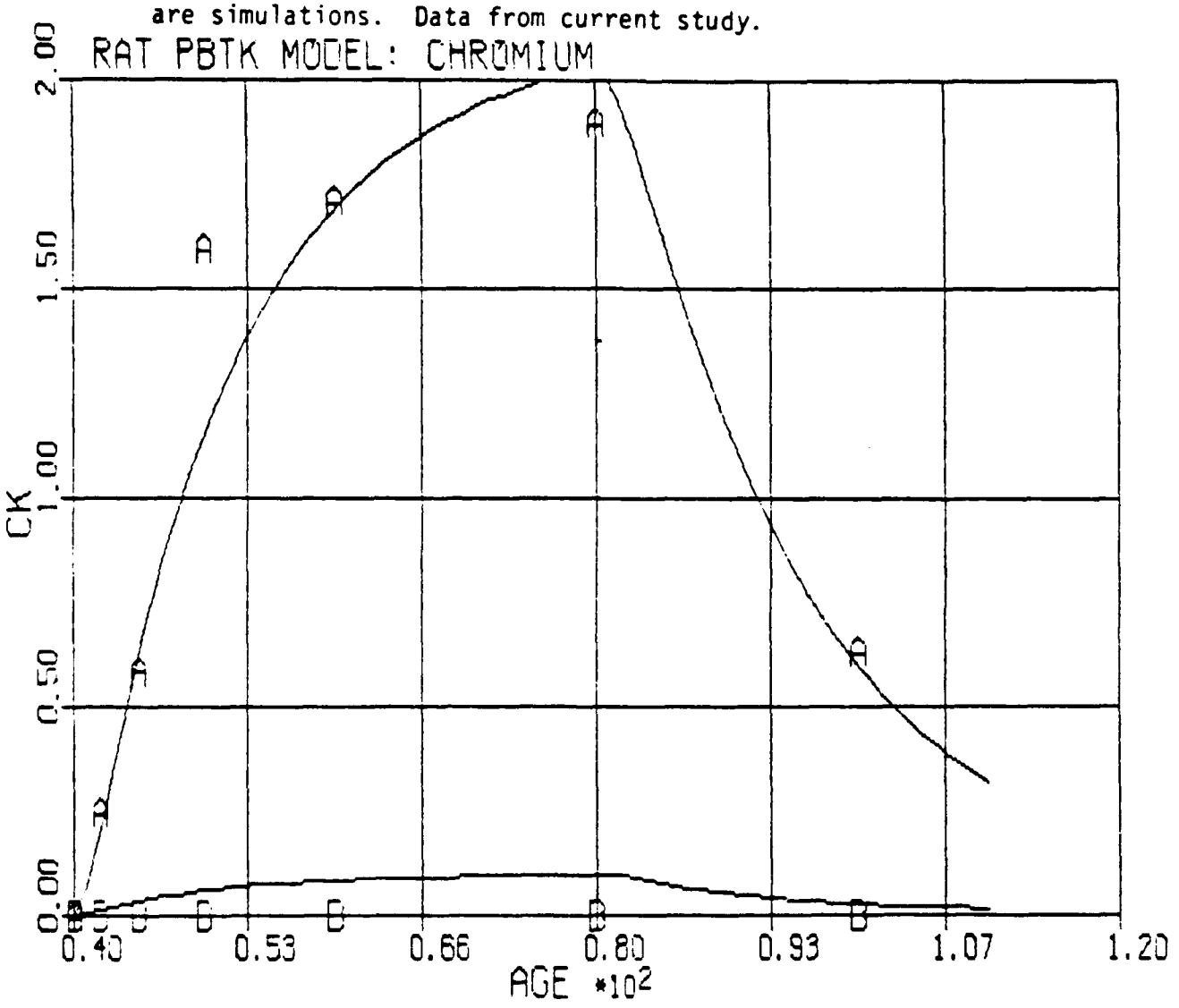


FIGURE 10

Rate of chromium excretion in urine during and after daily oral administration of Cr(III) (lower line) or Cr(VI) (upper line) for 40 days. Lines are simulations. Data from current study.

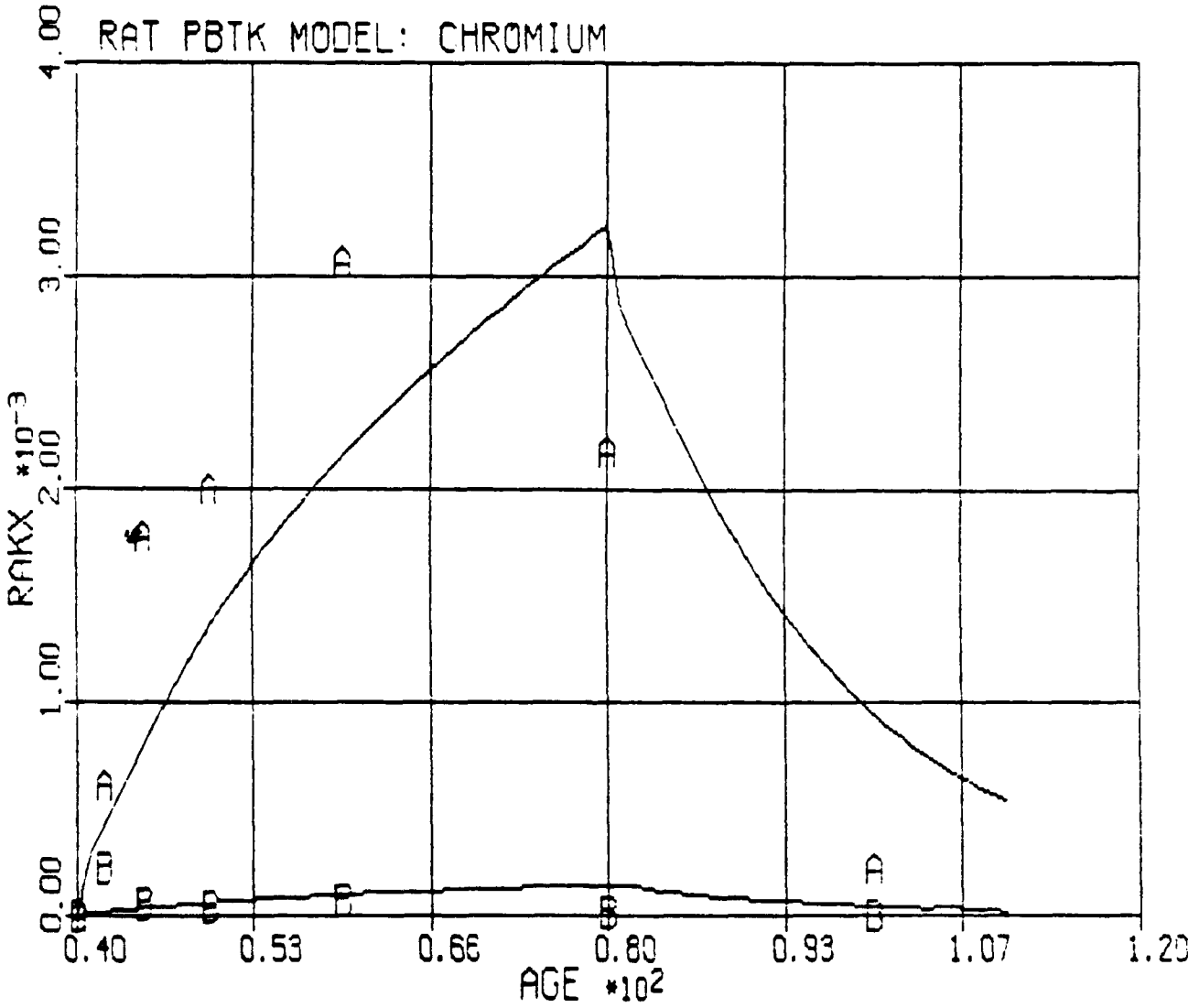


FIGURE 11

Rate of chromium excretion in feces during and after daily oral administration of Cr(III) (upper line; B) or Cr(VI) (lower line; A) for 40 days. Lines are simulations. Data from current study.

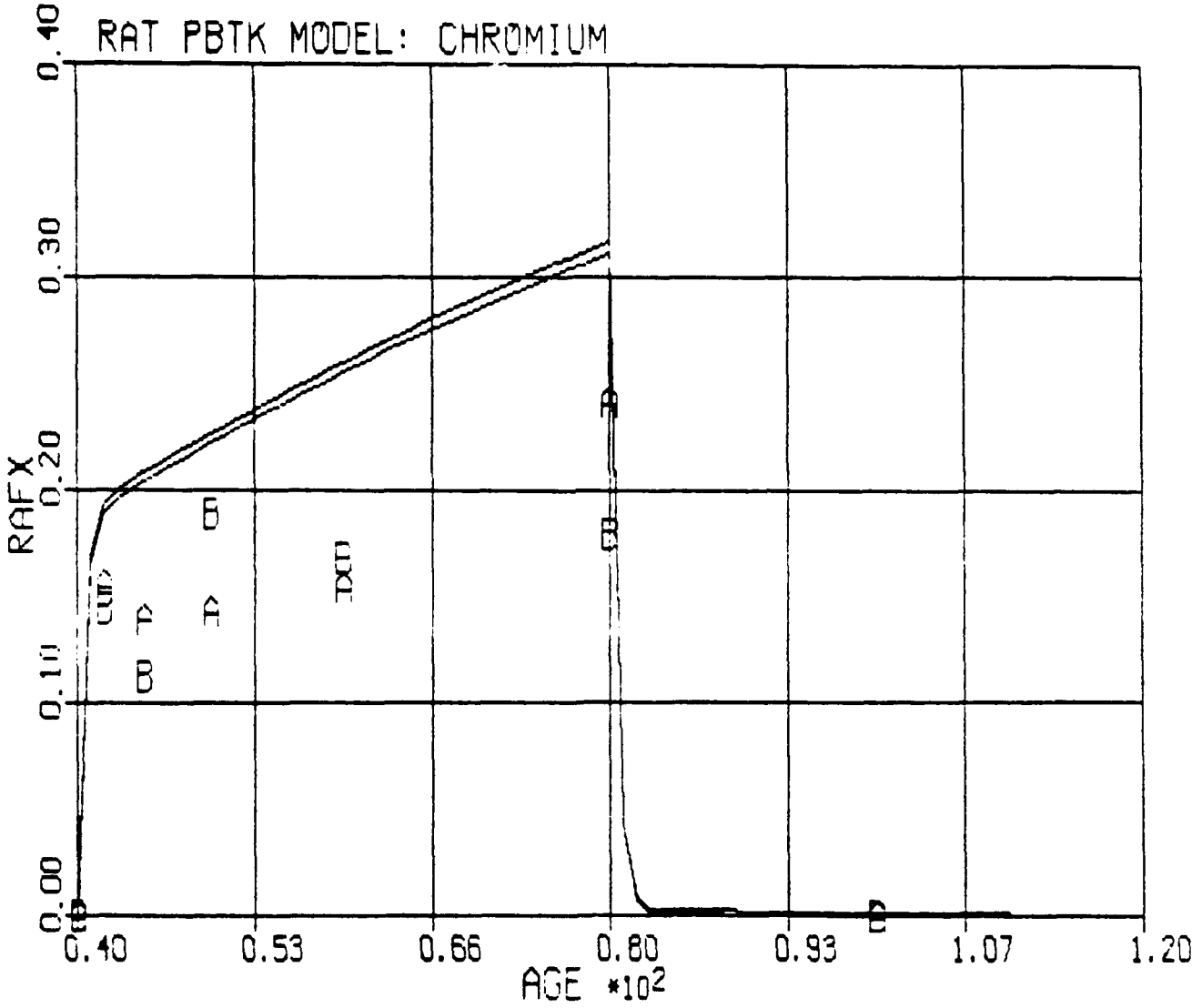


FIGURE 12

Chromium in blood during and after daily inhalation exposure to Cr(III) (B) or Cr(VI) (A) for 40 days. The line is the simulation for Cr(VI). Data from the current study.

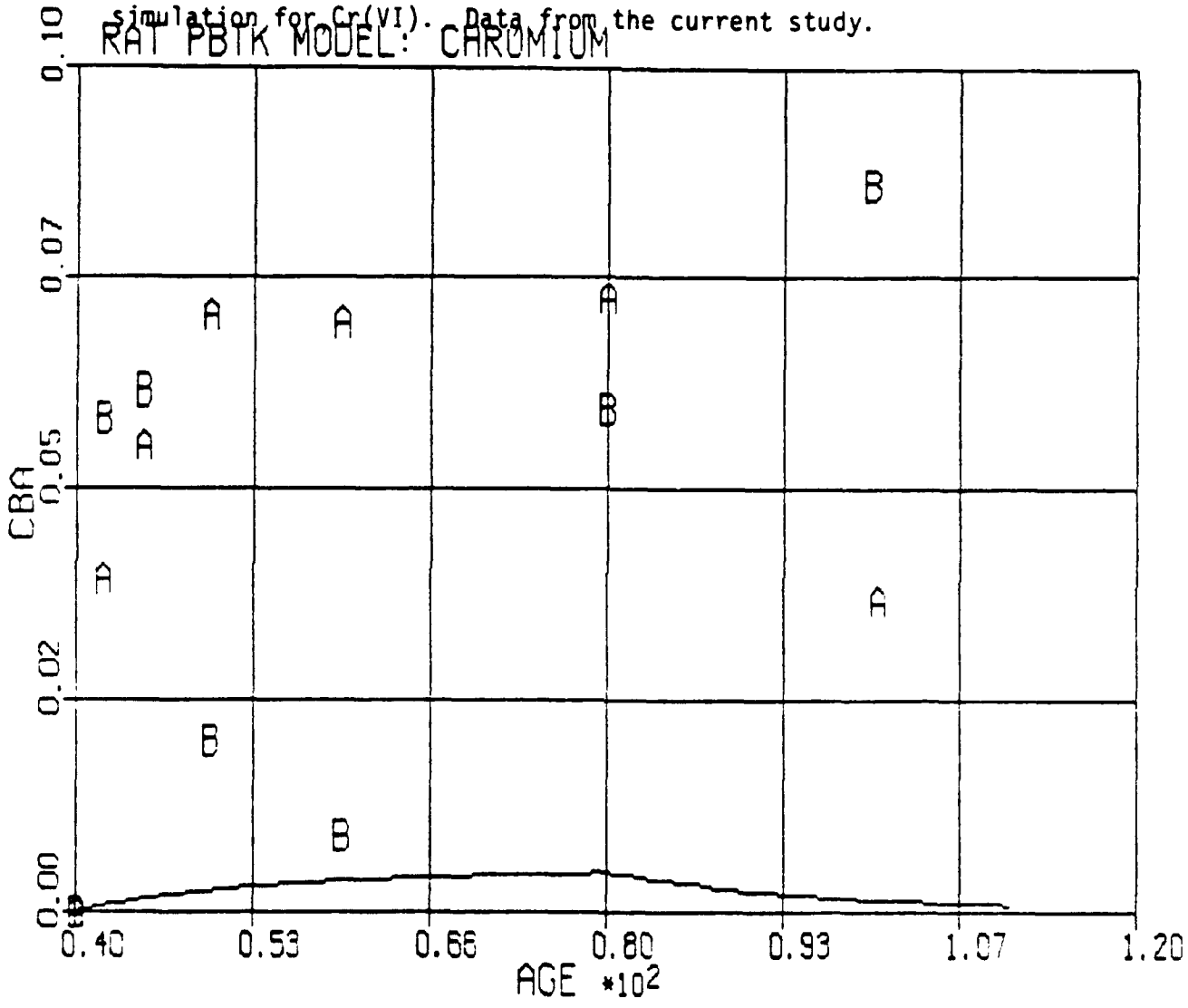


FIGURE 13

Chromium in lung during and after daily inhalation exposure to Cr(III) (upper line; B) or Cr(VI) (lower line; A) for 40 days. Lines are simulations. Data from the current study.

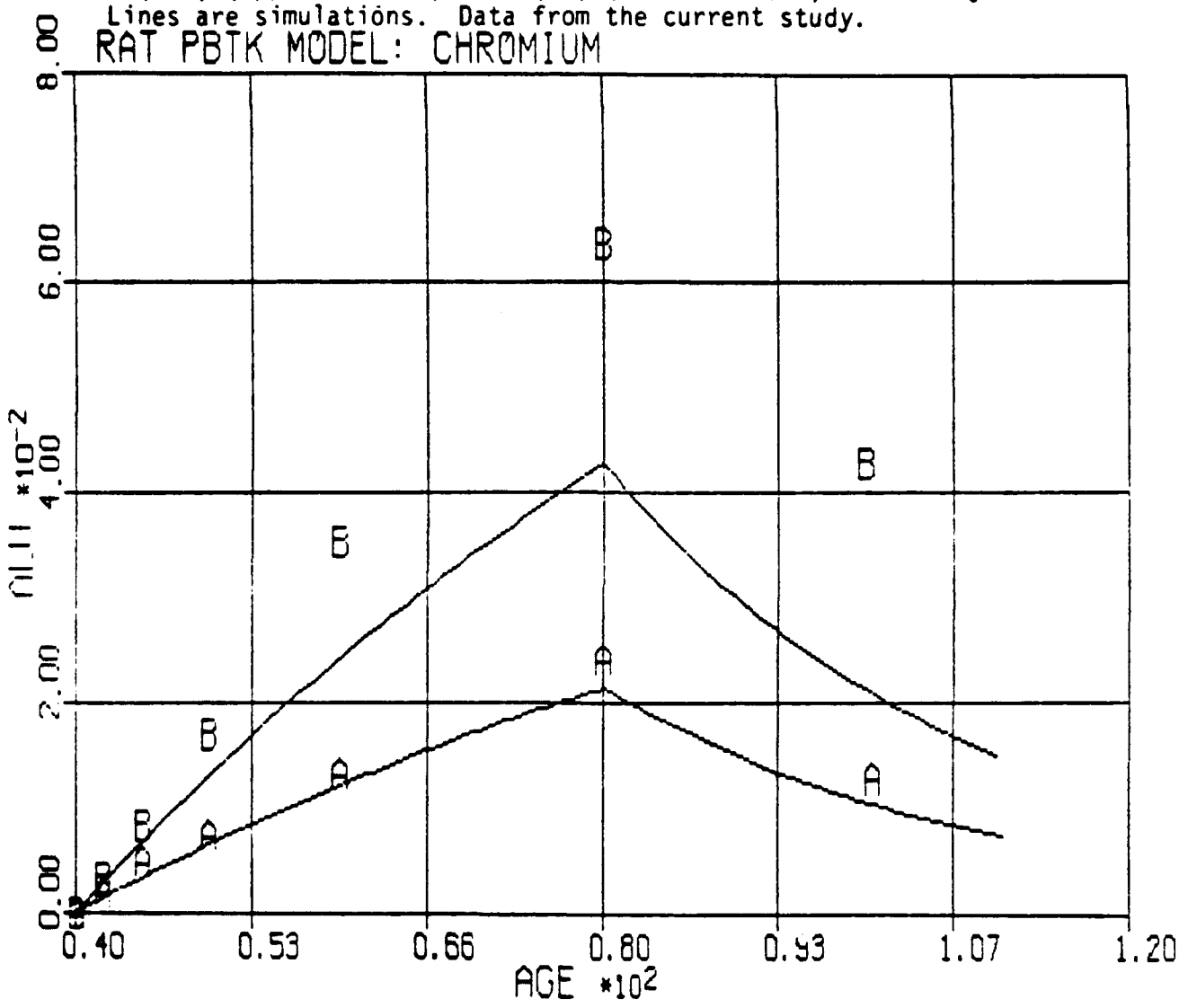


FIGURE 14

Chromium in liver during and after daily inhalation exposure to Cr(III) (lower line) or Cr(VI) (upper line) for 40 days. Lines are simulations. Data from the current study.

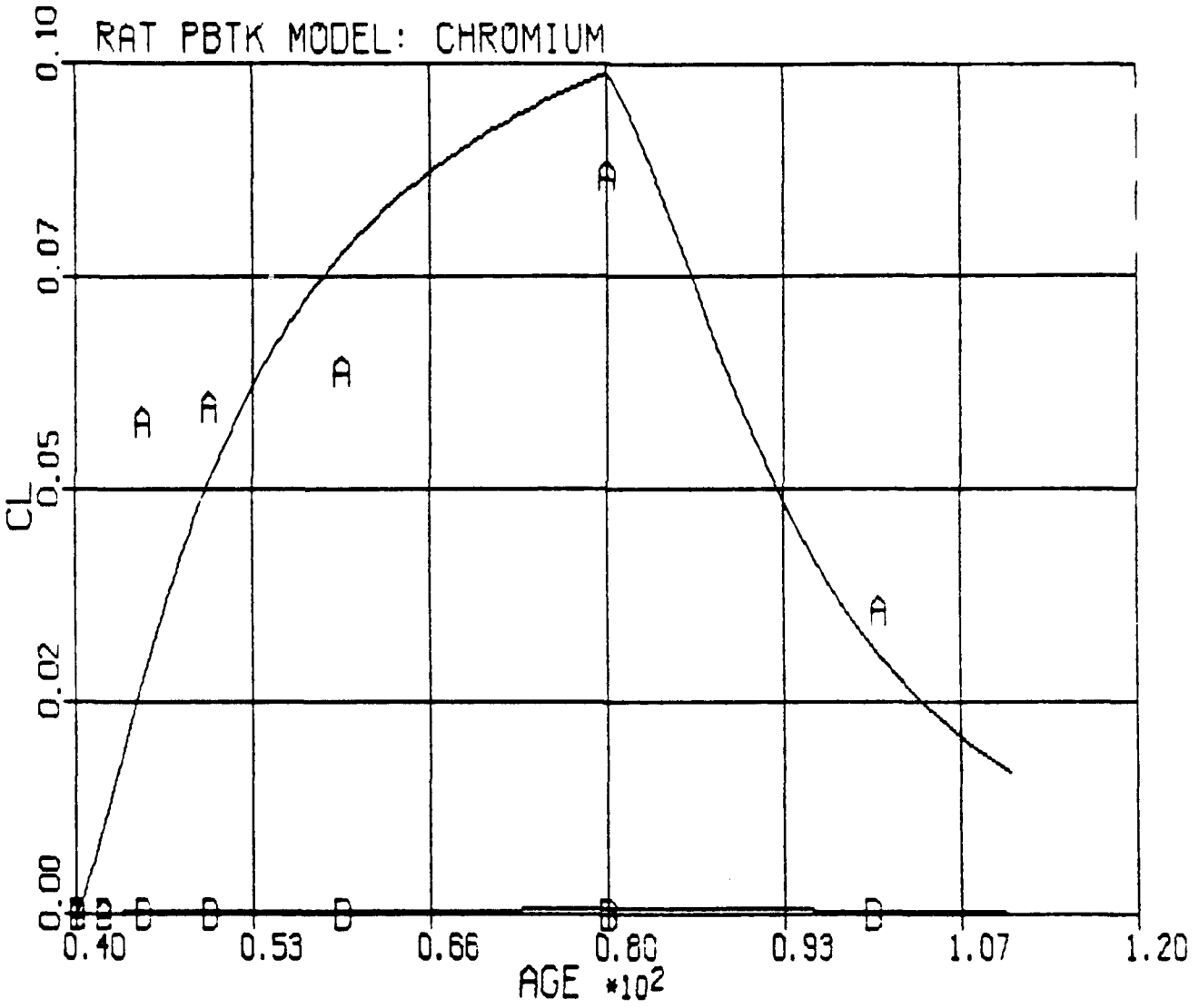


FIGURE 15

Chromium in kidney during and after daily inhalation exposure to Cr(III) (lower line) or Cr(VI) (upper line) for 40 days. Lines are simulations. Data from the current study.

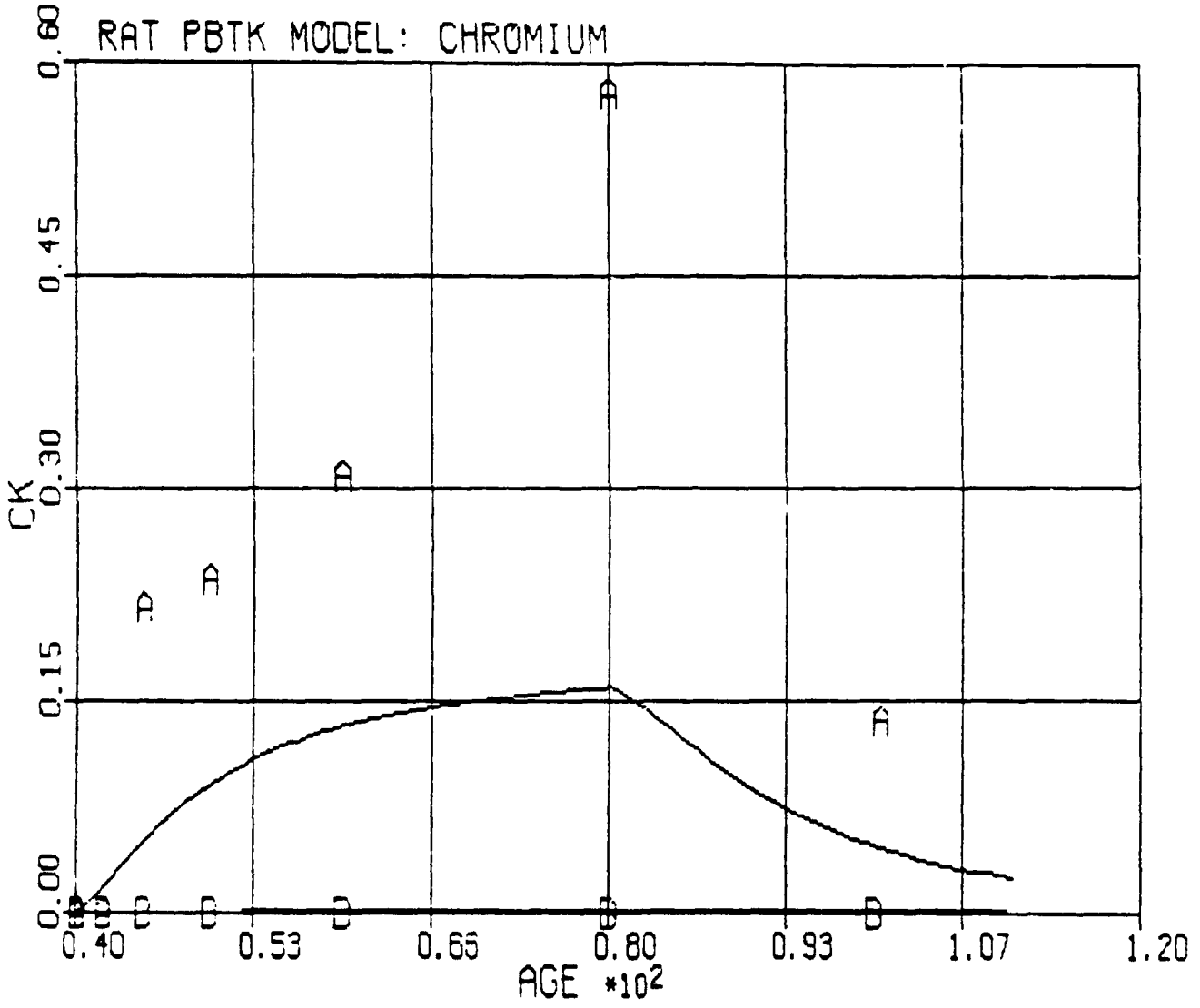


FIGURE 16

Rate of excretion of chromium in urine during and after daily inhalation exposure to Cr(III) (lower line) or Cr(VI) (upper line) for 40 days. Lines are simulations. Data from the current study.

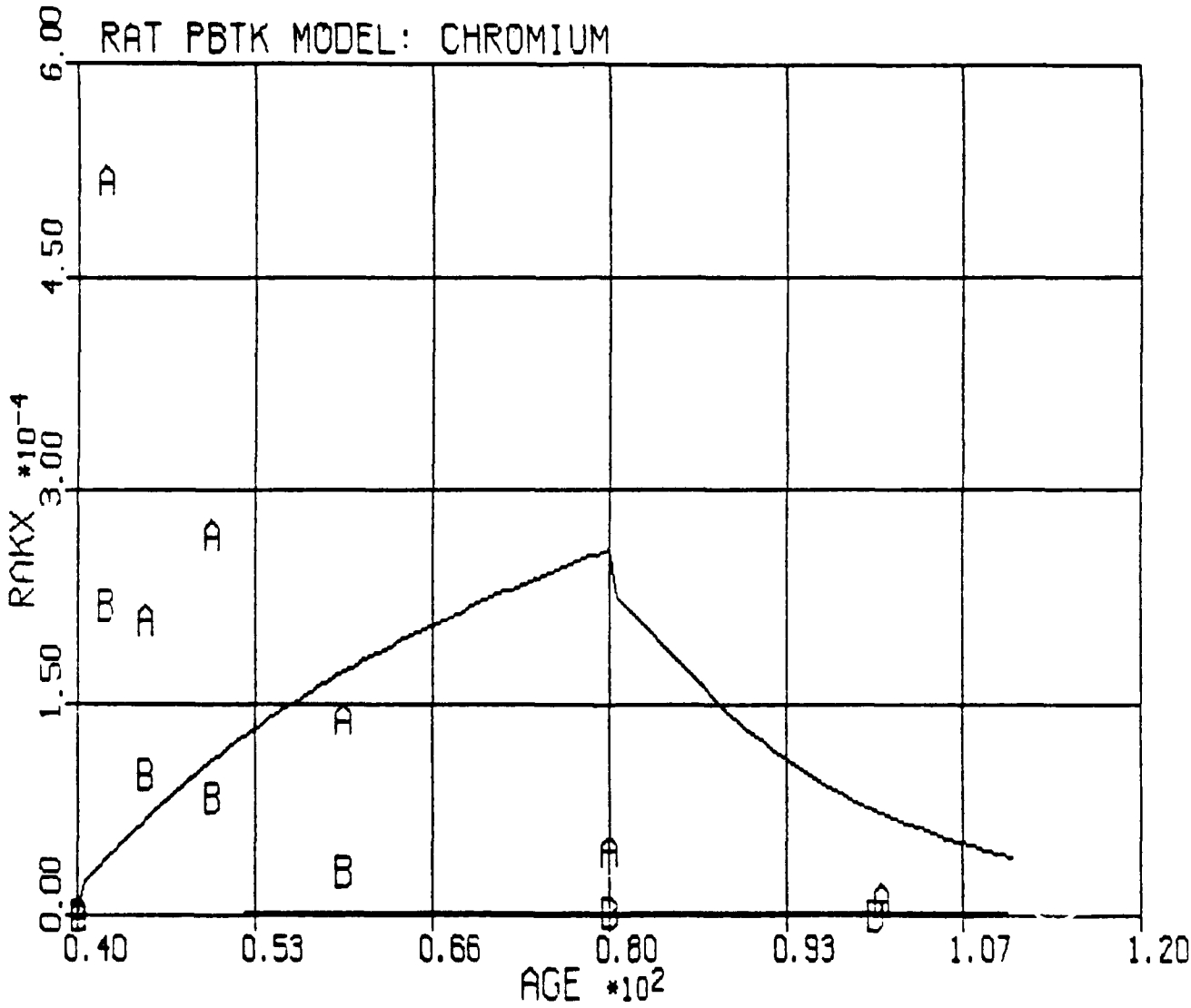
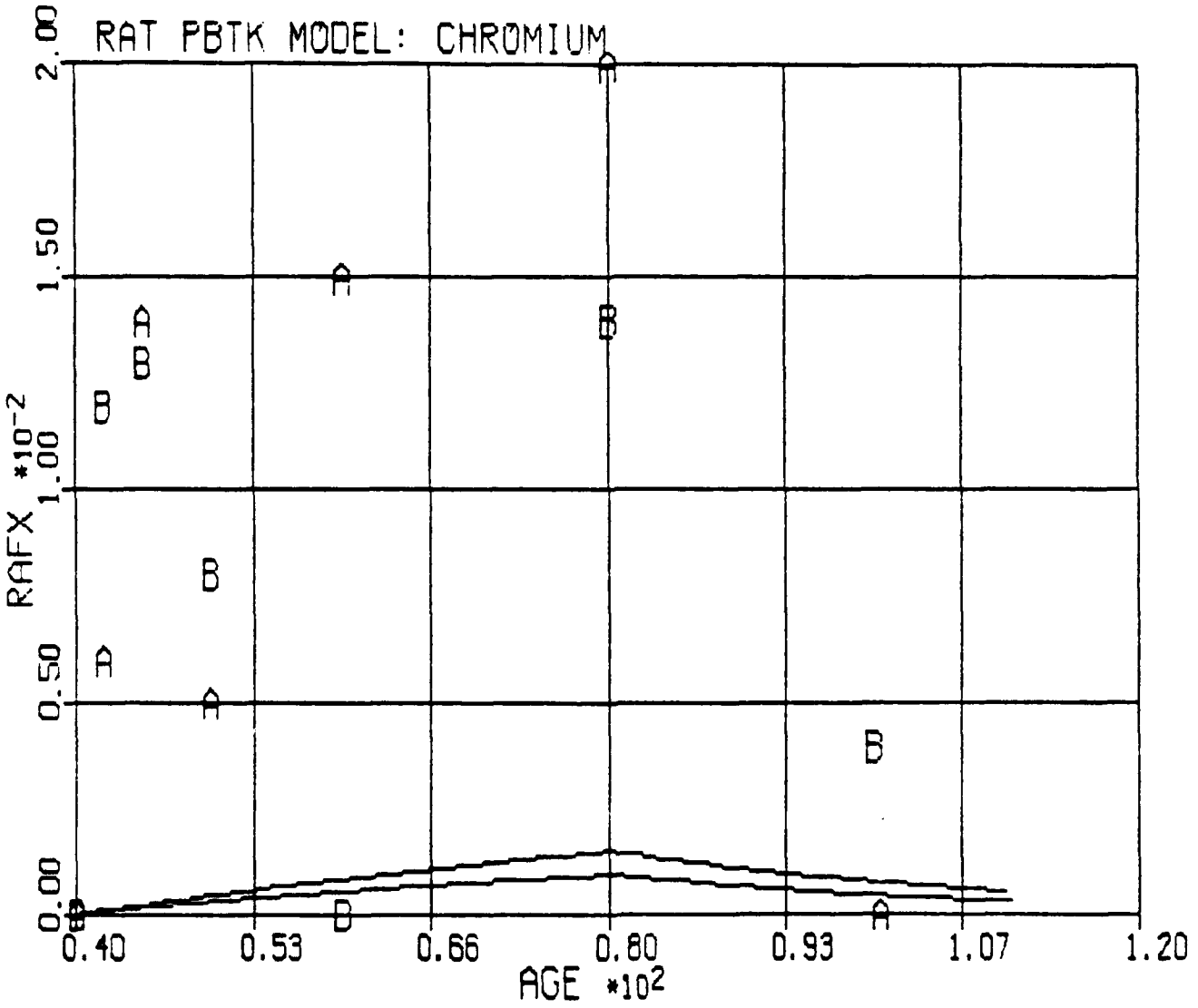


FIGURE 17

Rate of excretion of chromium in feces during and after daily inhalation exposure to Cr(III) (upper line; B) or Cr(VI) (lower line; A) for 40 days. Lines are simulations. Data from the current study.



III. EXPERIMENTAL STUDY IN RATS

A. METHODS

Chemicals: Sodium dichromate (99%) and chromic chloride-hexahydrate (99.9%) were obtained from Aldrich Chemical Company. Nitric and sulfuric acids and other chemicals were obtained from Fisher Scientific or Aldrich Chemical Co.

Animals: Male Sprague-Dawley rats (6 weeks of age) were purchased from Harlan, Indianapolis, Indiana. Rats were marked, weighed and quarantined for a minimum of two weeks prior to subchronic exposure. Eight rats were used in a pilot study and 216 in the 60 day experimental protocol. Animals were housed in AAALAC approved quarters with a light, humidity, and temperature controlled environment (lights on 0700-1900 hours; 50% + 5%; 23 + 1°C, respectively) and supplied with Purina lab chow and water ad libitum in groups receiving chromium compounds in water. Water and food were withdrawn from animals while they were in inhalation chambers (6 hrs/day).

1. Aerosol Generation

Chromium aerosols were generated from solutions of chromic chloride-hexahydrate (III) and sodium dichromate (VI) (Milli-Q) by jet ultrasonic jet nebulizers. Particles were passed through a ^{210}Po source to neutralize the electrical charge on particles. Aerosol concentrations were adjusted to 200 $\mu g/m^3$ by diluting the aerosol stream with filtered air. Mass median aerodynamic diameter of both aerosols were determined with a Mercer impactor. The Cr(III) aerosol MMAD was 0.9 $\mu \pm$ 0.28, 80% respirable and the Cr(VI) MMAD was 1.0 $\mu \pm$ 0.24, 63% respirable. Chromium concentrations were measured daily (AAS) and specific analysis for chromium VI was measured once a week by the diphenyl-carbizide method (NIOSH method 7600, 2/15/84). Chromium compounds were collected from chambers during exposure periods on 0.8 μm millipore filters by using calibrated sample pumps.

Both chromium solutions were analyzed for stability at various pH's over time prior to animal exposures.

2. Stability of Cr VI and III in Solution

Solutions of sodium dichromate ($Na_2Cr_2O_7 \cdot 2H_2O$) and chromic chloride ($CrCl_3 \cdot 6H_2O$) were prepared in deionized Milli-Q water at 2000 and 129 ppm Cr/L ($Na_2Cr_2O_7 \cdot 2H_2O$, valence VI; $CrCl_3 \cdot 6H_2O$, valence III). To obtain 2000 ppm Cr/L in both solutions, 5.7308 g/L of sodium dichromate (VI) and 10.2442 g/L of chromic chloride (III) were used. Both the 2000 and 129 ppm solutions (100 ml each) were titrated with 1 N or 0.1 N sodium hydroxide and tested for the stability of Cr VI and III at various pHs over time. Titrations of Cr VI, III and stability determinations were carried out twice.

At both concentrations, solutions at pH$\leq$6.6 were stable for one month. Solutions were not assayed for chromium content after one month. Speciation assays of Cr VI and III indicated that Cr VI is not reduced and Cr III is not oxidized in solution at one month. At a high pH (11.7) the Cr VI concentration decreased about 10% in one month; Cr III was stable.

At a pH of 10.03 or 9.9 the Cr III solution appeared to precipitate; the precipitate separated following centrifugation. Both Cr VI and Cr III solutions are colored; Cr VI is yellow and Cr III a blue green. The Cr VI solutions were clear at all pHs. Because Cr III solutions precipitated at high pHs, solutions at pHs of $\leq$6.6 were centrifuged; no precipitate was detected.

3. Exposure to Chromium in Drinking Water

The concentration of chromium in drinking water (deionized) was based on the dose calculated to be delivered by the inhalation route of exposure. Assuming that 80% of an inhaled dose was absorbed, the dose retained by one rat was calculated to be 7.344 µg/day/rat (resp/min = 85; tidal vol = 1.5 ml per 200 g rat). Assuming that 3% of ingested chromium was absorbed (chromium III, 0.5-3%, chromium VI 3-6%, WHO, 1988) and that a 200 g rat drinks 19 ml/day (16-22 ml), 12.9 mg of chromium per liter distilled water (chromium chloride or sodium dichromate) was chosen for a pilot study. A control group received distilled water. Food and water were provided ad libitum.

4. Exposure to Chromates by Inhalation

Based on values in published literature, 200 µg Cr/m3 was chosen for chamber concentrations as chromium using chromic chloride or sodium dichromate. Glaser et al. (1985) exposed rats to sodium dichromate from 25 to 200 µg/m3 for 28 or 90 days. Exposure duration was 22 hours/day, 7 days per week. In comparison to controls there were no differences in mean weight gain, histologic findings, red and white blood cell counts, serum activities of alanine aminotransferase, alkaline phosphatase, total cholesterol, creatinine or urea.

Animals (36 per treatment group) were placed in stainless steel holding cages and exposed to 200 µg Cr/m3 as chromic chloride (CrIII) or sodium dichromate (CrVI) or filtered air for 6 hrs/day, 7 days/week for 40 days. Food and water were withdrawn during exposure periods. When animals were removed from chambers they were placed in a dedicated animal room which is in the inhalation facility.

5. Collection of Urine and Feces

The afternoon before sacrifice two animals from each group were placed immediately in metabolism cages for the collection of urine and feces for 17 hours before days 2, 5, 10, 20, 40 and 60. Because of the limitation placed on urine and feces collection by the inhalation protocol, those animals receiving chromium compounds in drinking water were also placed in metabolism cages for collection of urine and feces for 17 hours before days 2, 5, 10, 20, 40 and 60. The number of metabolism cages available for this study were 12.

6. Necropsy, Tissue Collection and Storage

At the time of necropsy, anesthesia was administered to animals by trained personnel (5% sodium pentobarbital 90 mg/kg) and blood taken by cardiac puncture. Tissues were removed (whole blood, lung, liver, kidneys, intestines, muscle, carcass, urine, and feces), rinsed with physiological saline, patted dry, weighed, frozen in liquid nitrogen, wrapped in foil and frozen at -20°C until acid digested in preparation for quantitative analysis by AAS.

7. Analytical Techniques

Tissues were thawed and prepared for AAS by digestion and ashing. Techniques developed in our laboratory indicate that hydrochloric acid should not be used in acid digestion of tissues being analyzed for chromium content because losses occur during the ashing process. The AAS technique was used for total chromium content. To quantitatively determine chromium VI content of tissues the NIOSH method 7600 (diphenylcarbazide) was used. Methods for chromium analysis are detailed in the NIOSH Environmental Health Analytical Manual.

The chromium content in the blood and urine were quantified by Inductively Coupled Plasma - Mass Spectrometry (ICP-MS). The instrument was a VG PlasmaQuad and sample introduction was accomplished by solution nebulization.

B. EXPERIMENTAL DESIGN

Male Sprague-Dawley rats (216-36 per 6 treatment groups) were exposed via drinking water and inhalation to water soluble trivalent and hexavalent chromium compounds, chromic chloride-hexahydrate and sodium dichromate, respectively (Table I). An inhalation control group was placed in a chamber and exposed to filtered air for the same time period as chromium treated animals (6 hrs/day). A second control group received deionized water (no chromium) and was housed in the same room with rats ingesting water containing chromium compounds. All exposures were terminated on day 40. Thirty-six animals (six from each of six treatment groups) were sacrificed following days 2, 5, 10, 20 and 40 of exposure. The 36 rats remaining after the 40 day exposure period were allowed to live untreated twenty days longer (60 days from first exposure) to ascertain if there were clearance differences among treatment groups. Rat tissues (urine, feces, kidney, blood, liver, muscle, lung, intestine, carcass) were analyzed for chromium content.

Table I. Experimental Protocol[a]

	Trivalent[c]	Hexavalent[d]	Control
Inhalation[b] (6 hrs/day, 40 days)	200 µg Cr/m3	200 µg Cr/m3	Filtered Air
Drinking Water[b] (ad libitum, 40 days)	12.9 mg Cr/L	12.9 mg Cr/L	Water

[a]Each group contained 36 rats. Six animals from each group were sacrificed following days 2, 5, 10, 20 and 40 of exposure. The 36 exposed animals remaining were sacrificed after a 20 day recovery period.
[b]One concentration
[c]Chromic chloride-hexahydrate
[d]Sodium dichromate

C. RESULTS

When Cr(VI) was administered to rats in the drinking water, after 40 days the amount of chromium in the liver was approximately 20 times more than when Cr(VI) was administered by the inhalation route (Figures 1 and 2). Chromium (III) administered by either route was at or below the limit of detection of the analytical technique.

The reverse was observed in the lung after 40 days of exposure to Cr(VI); inhaled chromium was approximately 34 times greater than that found in the lung when Cr(VI) was ingested (Figures 3 and 4). Ingested Cr(III) varied from below the sensitivity of the assay to approximately 0.24 μg/g lung. The lungs of animals drinking Cr(VI) water contained a small concentration, about 0.4 μg/g tissue after 40 days of exposure. Inhaled Cr(III) vs Cr(VI) indicated that Cr(III) is poorly absorbed and Cr(VI) was absorbed to a greater extent. Cr(III) appears to be cleared more rapidly than Cr(VI).

Feces were collected from 2 animals per group per time point. Data for μg Cr/g wet weight are reported in Figures 5 and 6. As expected, the feces from animals drinking water containing chromium were high in both Cr(III) and Cr(VI). Twenty days after exposures ended, chromium in the feces returned to the level of control animals. In the feces of animals inhaling both chromium species it was evident that Cr(III) was slightly higher in the feces than Cr(VI); fecal chromium represents clearance from the lung over time. The intestinal data (Cr(VI) inhaled) make this even clearer (Figure 7) because the scale (μg Cr/g tissue) is expanded. Data for both chromium species (in water) were similar ranging from 14 μg Cr/g intestine to 29 μg Cr/g intestine.

The method for homogenizing the carcass was not appropriate for this study. After exposures were completed, Dr. C.M. Witmer's (personal communication) research indicates that Cr(VI) is sequestered in the bone. The results in the carcass suggest that when the homogenized sample contained some bone, the values were very high. The muscle data indicate there was a very small contribution of chromium to the carcass by muscle.

Figure 1

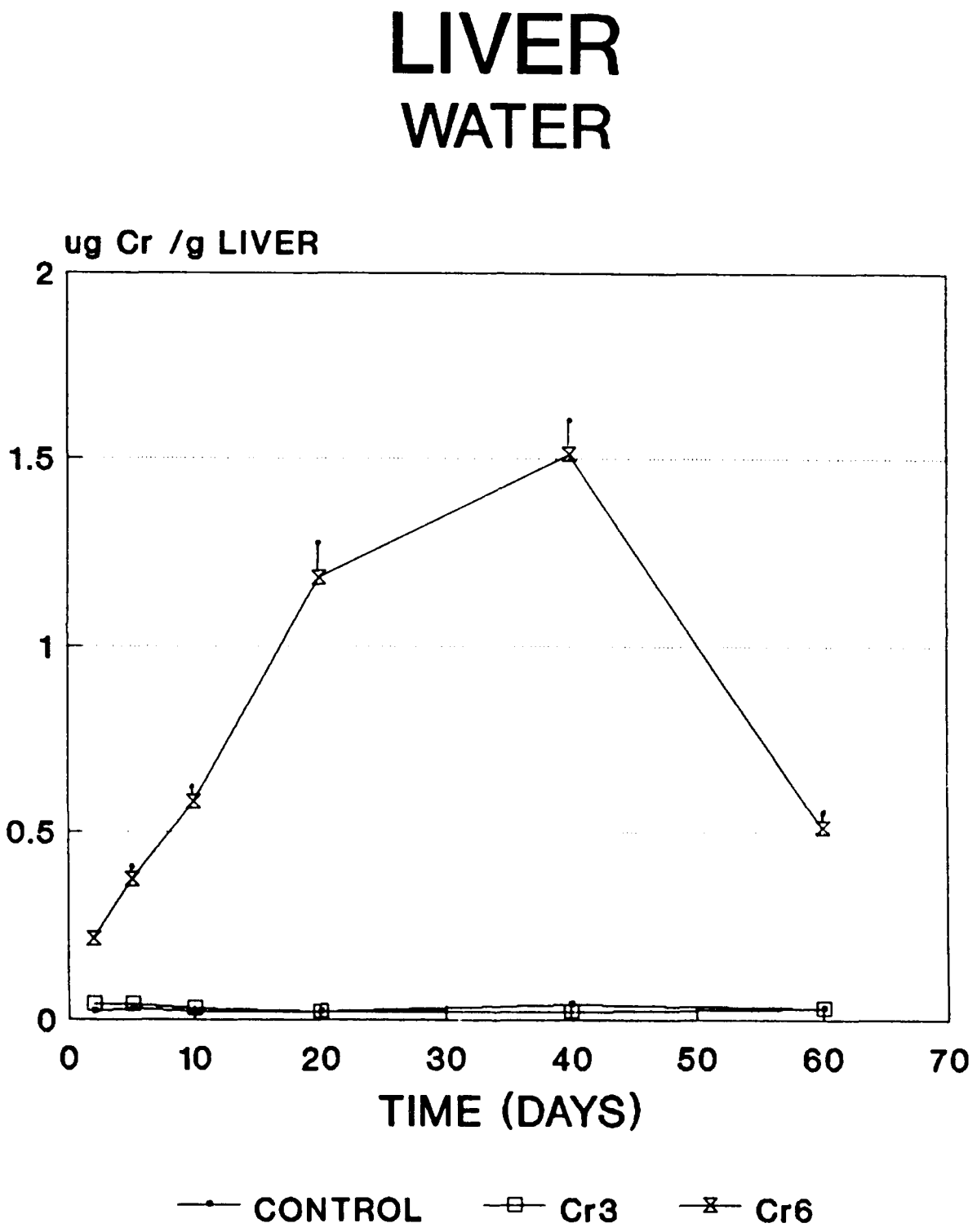

LIVER
WATER
ug Cr /g LIVER
2
1.5
1
0.5
0
0
10
20
30
40
50
60
70
TIME (DAYS)
CONTROL
Cr3
Cr6

Figure 2

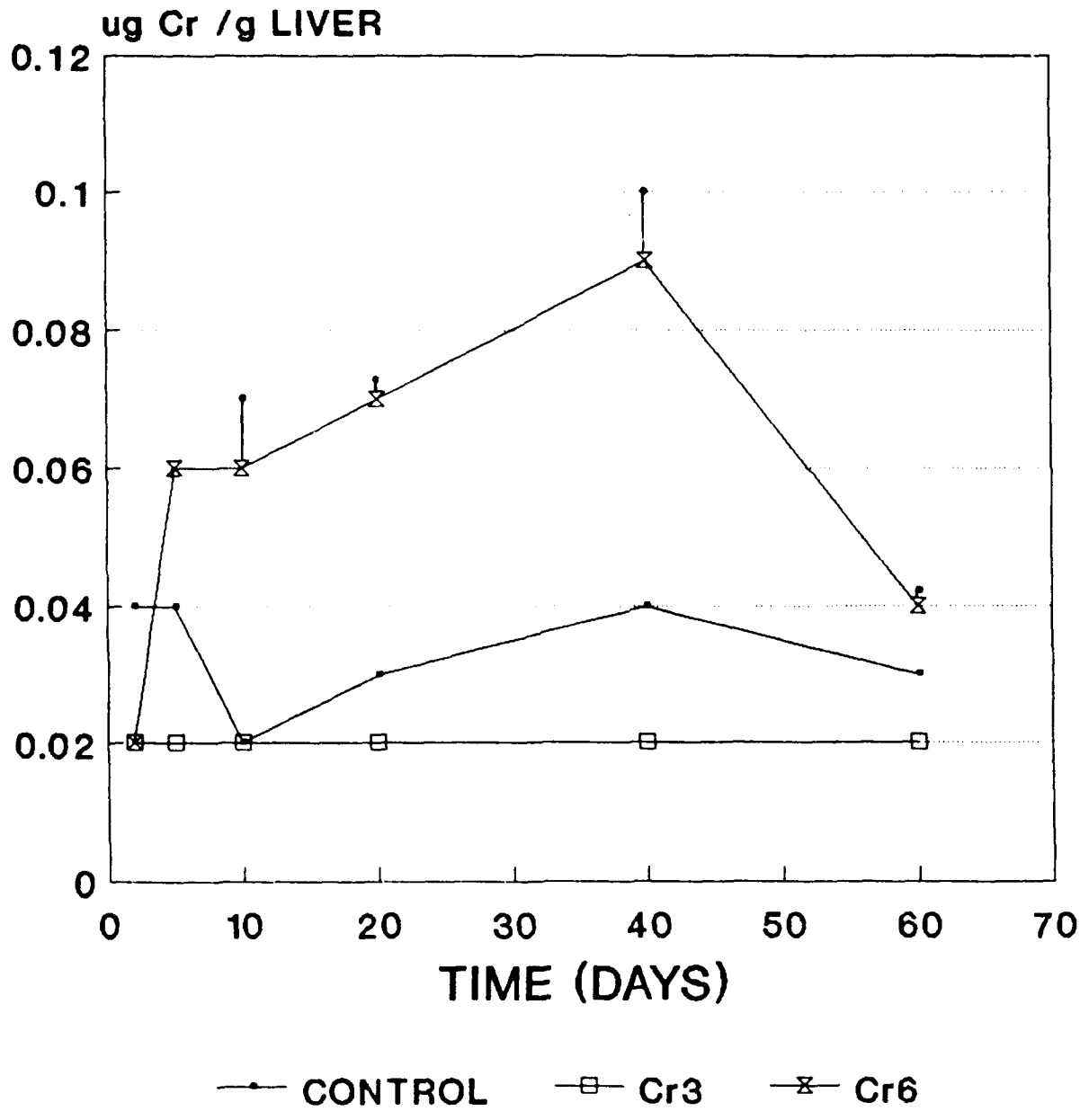

LIVER
INHALATION
ug Cr /g LIVER
0.12
0.1
0.08
0.06
0.04
0.02
0
0
10
20
30
40
50
60
70
TIME (DAYS)
CONTROL
Cr3
Cr6

Figure 3

LUNG
WATER

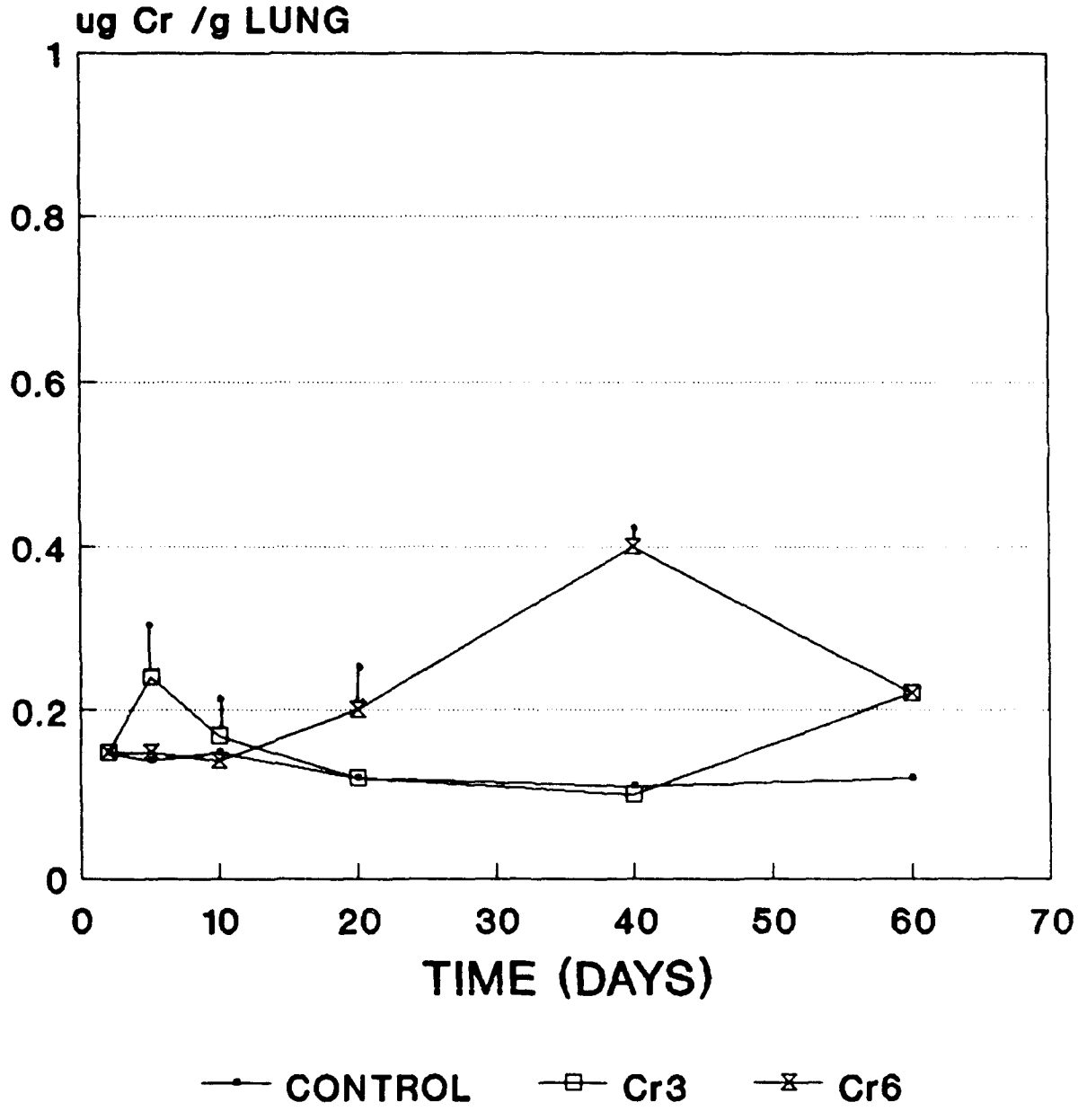


Figure 4

LUNG
INHALATION

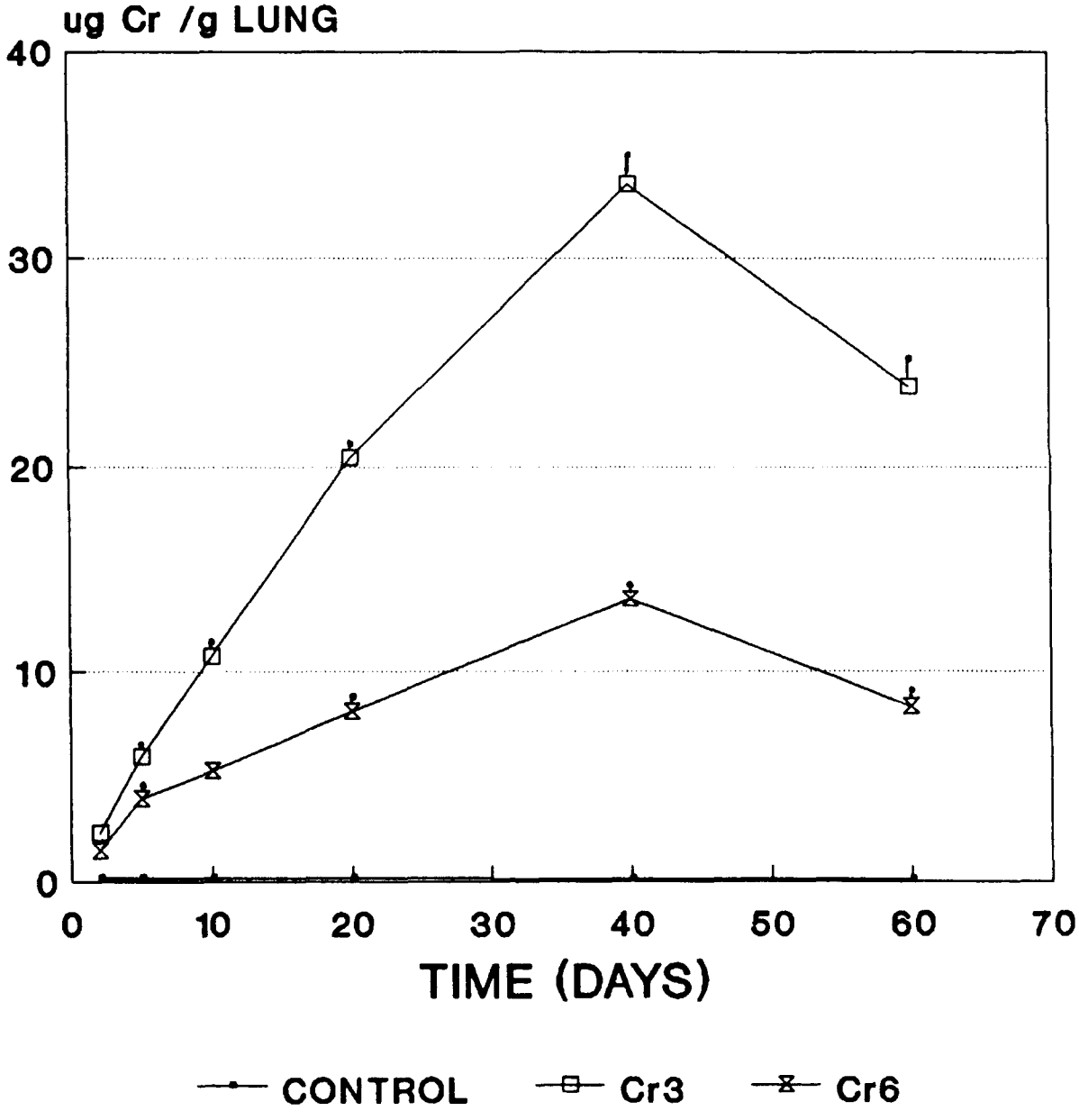


Figure 5

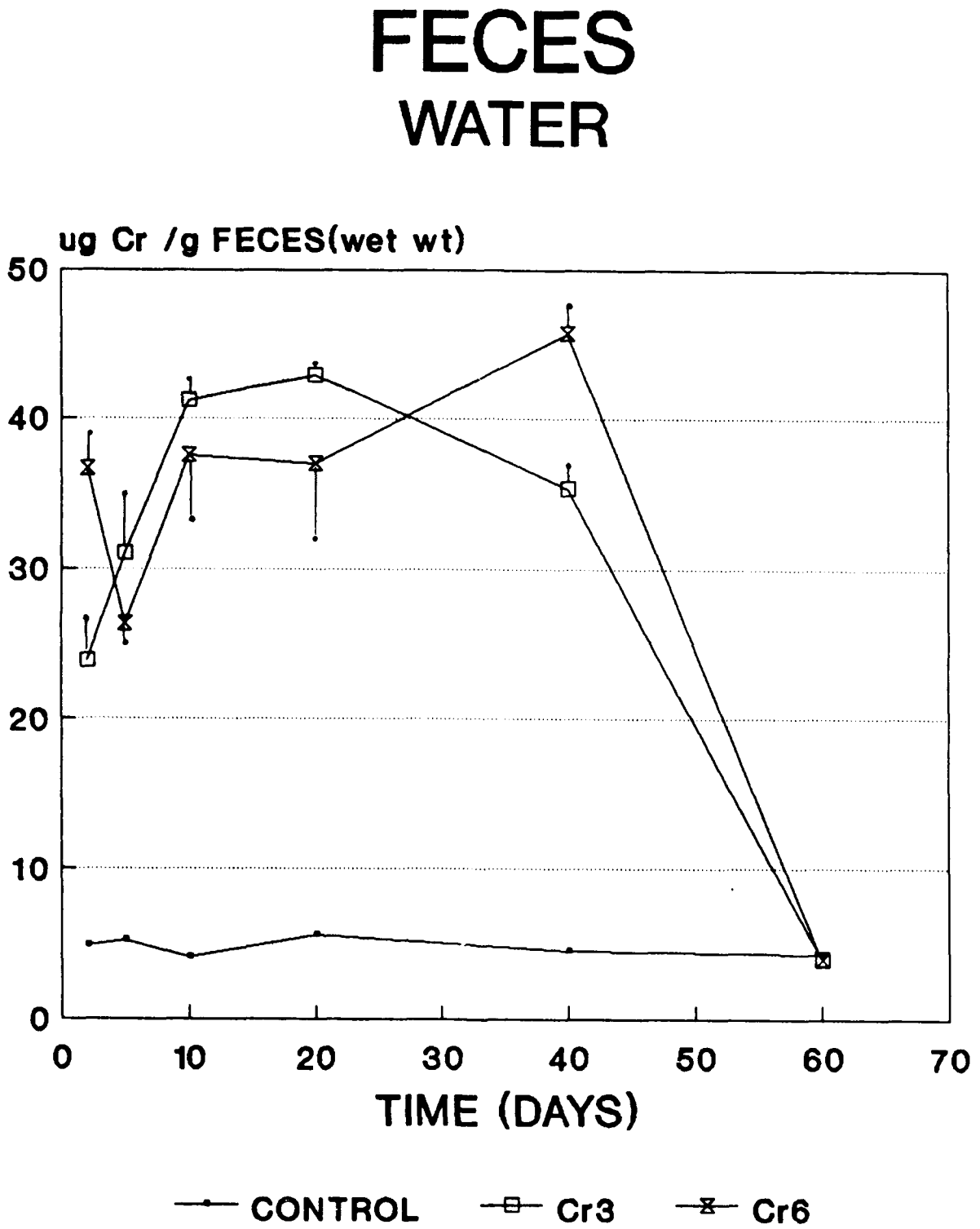

FECES
WATER
ug Cr /g FECES(wet wt)
50
40
30
20
10
0
0
10
20
30
40
50
60
70
TIME (DAYS)
CONTROL
Cr3
Cr6

Figure 6

FECES
INHALATION

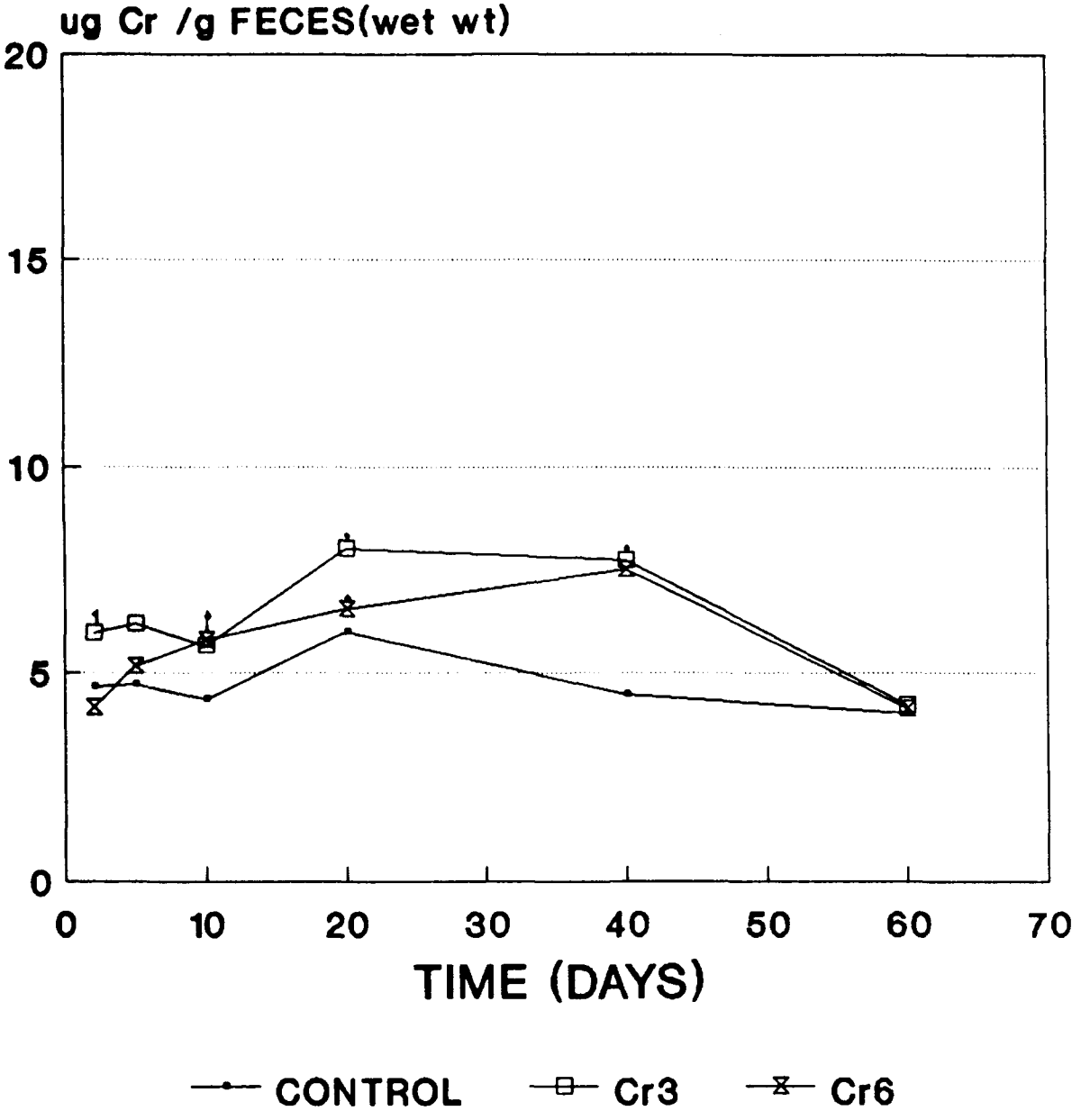
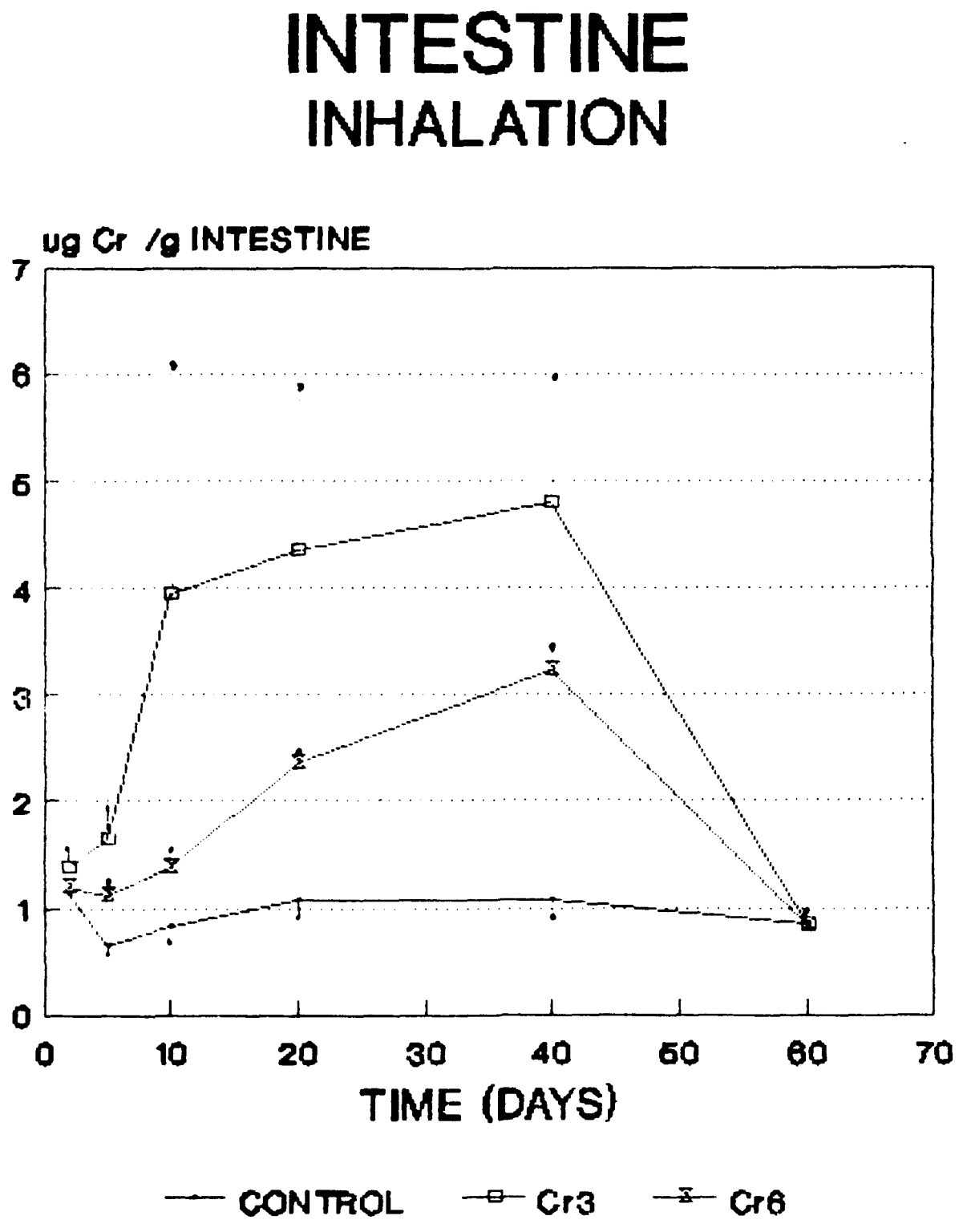


Figure 7


INTESTINE
INHALATION
ug Cr /g INTESTINE
7
6
5
4
3
2
1
0
0
10
20
30
40
50
60
70
TIME (DAYS)
CONTROL
Cr3
Cr6

IV. COMPARISON OF MODEL PREDICTIONS WITH EXPERIMENTAL DATA

The CHROMIUM.CMD file submitted on diskette and as part of Appendix B contains several simulation procedures for published studies (Mertz et al., 1965; Hopkins et al., 1965; Visek et al.,1953; Weber, 1983; MacKenzie et al., 1958). In addition, there are two procedures, ORALKETT and INHKETT, that contain the exposure conditions and data (as chromium concentrations or amounts in tissues) from the current study. In these two procedures, L=liver, LU=lung, K=kidney, GI=intestinal tract (without contents), U=urine, B=blood, and F=feces. Entry of "1.E10" for a data point indicates that the value was below the analytical detection limit.

All these procedures may be run from the simulation model file CHROMIUM.CSL, and the outputs compared either with observations from the cited articles or with the data entered as part of the procedure itself. Note that the procedure "INITIAL" contains all the parameter values, and must be run before any of the experimental procedures.

Figure 1 is a model prediction for the conditions of Mertz et al (1964), superimposed on the data from the study.

Figures 2-6 are model predictions for the conditions of Weber (1983). Percent of dose is simulated over a 40-day period in (Figure 2) liver, (Figure 3) lung, (Figure 4) kidney, (Figure 5) intestine, and (Figure 6) whole body. It is apparent that there are rapid losses of chromium from the body during the first 24 hours that are not accounted for by the model in its present form, but that otherwise the Weber data are duplicated well.

Figures 7-11 are model simulations superimposed on data from the current oral study. In these figures, total chromium concentration is simulated in (Figure 7) blood, (Figure 8) liver, and (Figure 9) kidney, as well as rate of excretion in (Figure 10) urine and (Figure 11) feces.

Figures 12-17 are model simulations superimposed on data from the current inhalation study. In these figures, total chromium concentration is simulated in (Figure 12) blood, (Figure 13) liver, and (Figure 14) kidney, as well as rate of excretion in (Figure 15) urine and (Figure 16) feces. The blood data are not well predicted, but the discrepancy is believed to be due to analytical problems with high reagent blanks in these groups (see Section IIA, above). Otherwise, the inhalation data are satisfactorily described by the same set of parameter values used in the Weber (1983) simulation for rats given a single dose of Cr(VI) by intratracheal administration.

V. DISCUSSION

The kinetic behavior of chromium is very complex, depending as it does on the solubility of the compound administered, the oxidation state of the chromium, the route of administration, and partitioning of chromium between the red cell and the plasma. Rates of absorption, of reduction of Cr(VI) to Cr(III), and of uptake by tisues including the red cell, are in a delicate balance, and a small change in the rate of any one of these processes may cause a profound shift in this balance and a very different kinetic pattern. The processes that have been incorporated into the physiologically-based chromium kinetic model are believed to be the key processes determining chromium kinetics, but their relative magnitudes - that is, the values of many of the parameters that characterize them - are still fairly uncertain. For example, the rate constant for reduction of Cr(VI) to Cr(III) has been set at the same value for all tissues including the red cell, whereas in fact it is quite probably tissue-dependent and may well depend also on the animal's nutritional and metabolic status.

The key processes are differential absorption from the lung and GI tract (differential abilities to cross membranes); rapid reduction of Cr(VI) to Cr(III) in all tissues and less rapid reduction in the GI tract contents; flow-limited tissue uptake of Cr(VI), which readily crosses membranes, and diffusion-limited uptake of Cr(III), which does not; uptake of Cr(VI) by red cells, its subsequent reduction and return to the systemic circulation as Cr(III); and incorporation of chromium to a moderate but significant extent into forming bone. There is solid experimental basis for the qualitative importance of all of these processes, but little experimental basis for the relative or absolute magnitude of many of them.

The distribution and persistence of Cr(III) salts in tissues such as liver, kidney, bone marrow, and spleen suggested to early investigators that intravenously-administered Cr(III) could form a colloid that was taken up by the reticuloendothelial system. Certainly the tissue distribution of intravenously-administered Cr(III) salts was shown to be markedly dependent on both the chemical and physical form of the compound given (Visek et al., 1953). This problem of speciation of intravenously-administered chromium extends to interpretation of published biliary excretion data, which are essentially from three studies in each of which Cr(III) or Cr(VI) was given intravenously. Cikrt and Bencko (1979) demonstrated that the cumulative biliary excretion of Cr(VI) after 24 hours was about 3.5% of the dose, compared with urinary excretion of about 21% of the dose. After intravenous administration of Cr(III), about the same fraction, 22%, had been excreted in the urine by 24 hours but only 0.5% in the bile. The difference is not due to restricted ability to excrete Cr(III) in bile. Cr(III) is readily excreted in the bile after Cr(VI) injection (Norseth et al., 1982); indeed, no Cr(VI) is found in the bile at all when Cr(VI) is given. Since bile itself does not reduce Cr(VI) (Norseth et al., 1982), it is most likely that Cr(III) generated in the liver by intracellular reduction of Cr(VI) is excreted in the bile. Cavalleri et al. 1985) confirmed that 99% of chromium in bile is in the form of Cr(III) even when Cr(VI) has been injected, and also confirmed the inability of bile to reduce Cr(VI) to Cr(III).

These observations concerning the dependence of chromium distribution and biliary excretion on speciation, particularly for intravenously-administered chromium salts, suggest that data taken from intravenous studies should be given less weight in development of a physiologically-based chromium model than data

from studies in which chromium was administered orally or by inhalation. Table 2, for example, demonstrates only fair agreement between the absolute magnitudes of observed and predicted uptake into bone, but it does show that the temporal trends of the amounts of chromium in bone are being predicted correctly. It is quite possible that the Cr(III) injected intravenously in the Hopkins (1964) study on which this comparison is based was still present in relatively large amounts in the bone marrow four hours after administration, contaminating the bone samples and resulting in the discrepancy between observed and predicted values.

The tendency for chromium to be lost more slowly from liver, spleen, and bone marrow than from other tissues has not been incorporated into the model. Only for the kidney has this prolonged retention been modeled. Spleen and bone marrow were not explicitly defined in the model, and the behavior of the liver was judged not to be sufficiently different from that of other soft tissues to warrant special treatment. Nonetheless, Cr(III) clearly displays different kinetic behaviors in different tissues, and the model is fairly crude in this regard. If the concentration of chromium in a particular tissue were to be of interest, the diffusion constants for diffusion of chromium into and out of the tissue should be more precisely defined than they now are. Use of diffusion constants, or clearances, to describe these transfers is consistent either with rate-determining intra-tissue binding or with rate-determining trapping of chromium by some other mechanism, as long as these processes are kinetically first-order.

Binding of chromium to macromolecules, and its association with low-molecular-weight ligands, also are not treated in the model. Too little is known about these linkages to make their inclusion possible. It is not even known whether dissociation of chromium from its binding sites may under any circumstances be kinetically rate-determining, although the low clearance values-by comparison with, say, the glomerular filtration rate in rats of 3-4 L plasma/da - suggest that this may be so. Sequestration of chromium by binding or other means, particularly in the lung where Cr(VI) can be carcinogenic, is an area with research potential.

The lung is much more complex kinetically than its representation in the present model suggests, and several multicompartmental physiologically-based models of pulmonary kinetics have been designed. When interactions of lung compartmentalization with the differential solubilities and chemical properties of different chromium salts are considered, it is apparent that more detailed models would become unwieldy rather quickly. More to the point, however, our current quantitative understanding of clearance of chromium from the lung does not support development of other than a simplistic model of pulmonary chromium kinetics. In this simple model, comparable magnitudes of the first-order rate constants for systemic absorption of Cr(VI) and for its reduction to Cr(III) were necessary in order to reproduce the observed kinetics. This implies that the behavior of inhaled Cr(VI) should be very sensitive to small changes in the rates of either of these pathways.

Deposition in the lung of only 5% of either inhaled Cr(III) or inhaled Cr(VI) accounts for all of the tissue chromium found, including chromium in lung tissue. However, this deposition figure results in a significant underestimate of the amount of chromium appearing in the feces (Figure 17). It is probable that some of the chromium inhaled was trapped in the nasopharynx or in the

trachea, from which sites it was cleared into the GI tract without ever having reached the lung itself. If this is the case, the model is underestimating absorption from the GI tract under these conditions. It is interesting that the values of the parameters that determine the magnitudes of both systemic Cr(VI) absorption from the lung and mucociliary clearance of chromium are the same, in the present model, as the values that were required to fit the data of Weber (1983), who gave a single intratracheal dose of Cr(VI). Thus, there is no suggestion that chronic administration alters the value of either of these parameters. In the Weber study also, the rapid loss of chromium from the lung and the whole body during the first few hours after intratracheal administration could have been due to its clearance from the trachea directly into the GI tract without reaching sites of potential absorption in the lung.

Wiegand et al. (1985) studied the kinetics of uptake of Cr(VI) into rat red cells by fast-reaction in vitro kinetics techniques. The longer of the two uptake half-lives they observed, 10 minutes, is shorter by two orders of magnitude than the half-life used in the present model. There is no obvious explanation for this large discrepancy, but it is clear that an uptake half-life of 10 minutes, coupled with the known 18-day half-life for release of chromium from the red cell, would result in unphysiological amounts of red cell chromium. It may simply be that the fast-reaction kinetics of small amounts of chromium are not representative of the kinetics of uptake of the much larger amounts considered in this model. It is also possible that migration of Cr(VI) out of the red cell can occur but is not seen because of the efficiency of the competing reduction mechanism.

Cr(III) clearances seem to be relatively consistent whatever the transfer process - into or out of tissues, or into or out of the body. The only exceptions are those tissues in which Cr(III) is apparently sequestered, prolonging its residence time. The same statement cannot be made about Cr(VI). Whole-body kinetics of Cr(VI) are predominantly determined by its rate of reduction to Cr(III), so that the magnitudes of other clearances are more or less immaterial to model predictions. The assumption that Cr(VI) kinetics are flow-limited is reasonable but is unverified.

The finding that bone chromium can be adequately modeled using a set of concepts developed for a chemically unrelated metal is encouraging. It illustrates one of the particular advantages of physiologically-based models: that they are adaptable across routes and patterns of exposure, and, as in this case, across chemicals provided that the physiological basis of the processes are adequately understood and accurately expressed.

The chromium model presented here incorporates several features not previously included in any complete (that is, whole-body) physiologically-based model. Mucociliary clearance from the lung is modeled. The contributions of mucociliary clearance, biliary excretion, and intestinal excretion to chromium in the gastrointestinal tract are considered so that enterohepatic circulation can be taken into account. The change in oxidation state of Cr(VI), to Cr(III), is also incorporated. And finally, exposure can be modeled to either or both oxidation states and by any or all routes: intravenous, oral, intratracheal, or inhalation.

The model in its present form has not been subjected to computerized optimization of parameter values. Before it is used for predictive applications,

both a sensitivity analysis and optimization of key parameter values, with careful attention to the variety of kinetic data bases available, should be undertaken.

ACKNOWLEDGEMENTS

We would like to thank the following people who contributed their time and effort to the successful completion of this project.

M. Wilson Tabor, Ph.D.
Director of Analytical Services

Herbert Kagen, Ph.D.
Analytical Services

Nick Gener
Ray Reilman
Chemical and Data Analysis; Data Management

Frank Grande
Conduct of Experimental Study

Leva Wilson
Secretarial Services

and

Jane Agee
Stacey Andringa
Jeff Dietz, Ph.D.
James Evans
Lynda Ewers
Frank Grande
Ray Reilman
Sandra Roda
Sharon Spalding

who worked together on the animal kills and preparation of tissues for storage and analysis.

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APPENDIX A

Flow Chart for Model Development

APPENDIX A

Flow Chart for Model Development

General structure of Cr(III) model taken from existing Pb model, with exclusion of any slow exchange in bone.

Visual fit of model predictions to data of Hopkins (1965) to obtain rough estimates of Cr(III) clearance between blood and soft tissues and its fractional clearance into forming bone (IV Cr(III) exposure, 4-day followup).

Extension of time frame of model predictions, using second half-life calculated by Mertz et al. (1965) to obtain an estimate of whole-body Cr(III) clearance. Comparison of model predictions of chromium body burden with data of Mertz et al. (1965) (IV Cr(III) exposure, 75-day followup, total body Cr only).

Incorporation of relative magnitudes of rapid surface exchange at bone surfaces and formation/resorption of bone in juvenile and mature rats based on data of Hopkins (1965) (IV Cr(III), bone data reported at 0.25, 4, and 24 hours).

Refinement of Cr(III) distribution parameters by comparison with data of Visek et al. (1953) (IV Cr(III), data reported at 4 and 42 days).

Addition of first-order reduction of Cr(VI) to Cr(III) based on Cavalleri et al. (1985). Comparison of model predictions with data of Visek et al. (1953) (IV Cr(III) and Cr(VI) exposure, data reported at 4 and 42 days). Note that Cr(VI) distribution is determined by blood flow alone.

Allocation of whole-body clearance to fractional clearances into bile and urine and across intestinal wall, according to observations of Cikrt and Bencko (1979), Norseth et al. (1982), and Cavalleri et al. (1985) (IV Cr(III) and/or Cr(VI); collection of bile (and by Cikrt and Bencko, urine and feces also) for up to 24 hours).

Addition of a red cell compartment in communication with arterial blood. Clearance of chromium from the red cell fixed on basis of measured half-life of red cell chromium (Bishop and Surgenor, 1964).

Expansion of IV model to include gastrointestinal uptake. Initial values of fractional uptake based on Visek et al. (1953) and MacKenzie et al. (1959) (Cr(III) or Cr(VI) given as single oral dose, absorption assessed by excretion in urine after 14 days or by tissue distribution in comparison to IV dose).

Adjustment of parameter values by visual optimization to fit data from this study (Cr(III) and Cr(VI) administered for 40 days in drinking water; Cr monitored in tissues, urine, and feces throughout exposure and at postexposure day 20).

Check against data of MacKenzie et al. (1958) (Cr(VI) and Cr(III) in drinking water; Cr measured in liver, kidney, bone, spleen after 1 year's chronic exposure).

Expansion of model to include uptake from lung. Initial values of rate constants for systemic absorption and for clearance into the GI tract taken from Weber (1983) (single intratracheal administration of soluble Cr(VI); Cr monitored in tissues, including whole body, for 40 days).

Final adjustment of parameter values by visual optimization to fit data from this study (Cr(III) and Cr(VI) administered daily, 5/7 days, by inhalation for 40 days; Cr monitored in tissues, urine, and feces throughout exposure and at postexposure day 20).

APPENDIX B

Printout of Physiologically-Based Model

```
PROGRAM: Physiological Toxicokinetic Model: Chromium in Rats'
'-------------------------------------------------------------'
'CHROMIUM.CSL'

INITIAL

'**Miscellaneous**'
ALGORITHM IALG=2 $ 'Gear integration algorithm for stiff systems'

'**Timing Commands**'
CONSTANT TSTOP=0.    $ 'Length of simulation (da)'
CONSTANT AGE0=0.     $ 'Age in days at which modeling is initiated'
AGEMO0=AGE0/30.5     $ 'Age in months at which modeling is initiated'
INTEGER EX           $ 'EX designates exposure'
ARRAY STEP(2)        $ 'Two conditions are distinguished: non-'
                       'exposure and exposure'
CONSTANT STEP=1.,.01
                       'Finer integration detail during exposure'
EX=1                 $ 'Initialize EX'


'**Physiological Parameters**'
CONSTANT HALF=0.     $ 'Exp(half-time for growth to adult weight)'
                       '(exp(agemo))'
CONSTANT WADULT=0.   $ 'Body weight of adult (kg)'
CONSTANT CONST=0.    $ 'Constant for continuing growth of adult'
                       'male rats (kg/mo)'

PROCEDURAL(WBODY0=1,1)
IF (AGEMO0.EQ.0.) GOTO ZERO0
GOTO NEXT0
NEXT0..CONTINUE
      WBODY0=.005+WADULT*(EXP(AGEMO0)-1.)/(HALF+(EXP(AGEMO0)-1.))...
      +CONST*AGEMO0
                       'Body weight at start of simulation (kg)'
GOTO LEAVE0
ZERO0..CONTINUE
      WBODY0=.005 $ 'Body weight at birth (kg)'
GOTO LEAVE0
LEAVE0..CONTINUE
END

CONSTANT QCC=340.    $ 'Cardiac blood output (L/da/kg)'
QC=QCC*WADULT**.74   $ 'Cardiac blood output in the adult (L/da)'

CONSTANT QLC=.25     $ 'Fraction cardiac output going to liver'
CONSTANT QKC=.17     $ 'Fraction cardiac output going to kidney'
CONSTANT QIC=.17     $ 'Fraction cardiac output going to GI tract'
QWC=.86-(QLC+QKC+QIC)
                       'Fraction cardiac output going to other'
                       'well-perfused tissues'
CONSTANT QBC=.03     $ 'Fraction cardiac output going to bone'
QPC=.14-QBC          $ 'Fraction cardiac output going to other'
                       'poorly-perfused tissues'

CONSTANT VLC=.04     $ 'Liver volume in the adult (L/kg BW)'
CONSTANT VKC=.01     $ 'Kidney volume in the adult (L/kg BW)'
CONSTANT VIC=.03     $ 'Volume of GI tract in the adult (L/kg BW)'
CONSTANT VWC=.10     $ 'Volume of well-perfused tissues, including'
                       'liver, kidney, and GI tract, in the adult'
                       '(L/kg BW)'
CONSTANT VPC=.90     $ 'Volume of poorly-perfused tissues,'
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                        'including bone, in the adult (L/kg BW)'

'**Bone Parameters**'
CONSTANT EXCH=.005    $ 'Fraction of bone in surface exchange'
                        'compartment'
CONSTANT MINFOR=.003
                        'Minimum fractional bone formation rate (1/da)'
CONSTANT ALPHA=.2     $ 'Exponential constant for rapid first-order'
                        'decline of fractional bone formation rate'
                        'with age (1/da)'
CONSTANT ALPHA0=.321
                        'Multiplicative constant for rapid first-'
                        'order decline of fractional bone formation'
                        'rate with age (1/da)'
BETA=.0235-.0005*HALF
                        'Exponential constant for slower first-order'
                        'decline of fractional bone formation rate'
                        'with age (1/da)'
BETA0=(.083-.001*HALF)*(.78+.7*WADULT)
                        'Multiplicative constant for slower first-'
                        'order decline of fractional bone resorption'
                        'rate with age (1/da)'


'**Chromium Parameters**'
CONSTANT KRED=40.     $ 'Rate constant for reduction of Cr(VI)'
                        'to Cr(III) in all tissues and fluids'
                        'except GI tract (1/da)'
CONSTANT KREDGI=2.    $ 'Rate constant for reduction of Cr(VI)'
                        'to Cr(III) in GI tract (1/da)'
CONSTANT WDINC=0.     $ 'Clearance of Cr(III) from blood into well-'
                        'perfused tissues (L/da/kg)'
WDIN=WDINC*WADULT**.74
                        'Clearance of Cr(III) from blood into well-'
                        'perfused tissues in the adult (L/da)'
CONSTANT PDINC=0.     $ 'Clearance of Cr(III) from blood into poorly-'
                        'perfused tissues (L/da/kg)'
PDIN=PDINC*WADULT**.74
                        'Clearance of Cr(III) from blood into poorly-'
                        'perfused tissues in the adult (L/da)'

CONSTANT WDOUTC=0.    $ 'Clearance of Cr(III) from well-perfused'
                        'tissues into blood (L/da/kg)'
WDOUT=WDOUTC*WADULT**.74
                        'Clearance of Cr(III) from well-perfused'
                        'tissues into blood in the adult (L/da)'
CONSTANT PDOUTC=0.    $ 'Clearance of Cr(III) from poorly-perfused'
                        'tissues into blood (L/da/kg)'
PDOUT=PDOUTC*WADULT**.74
                        'Clearance of Cr(III) from poorly-perfused'
                        'tissues into blood in the adult (L/da)'

CONSTANT KIN6=0.      $ 'Clearance of Cr(VI) from arterial plasma into'
                        'red cells (L/da)'
CONSTANT KOUT=0.      $ 'Clearance of Cr(VI) and Cr(III) from red cells'
                        'into arterial plasma (L/da)'

CONSTANT QEC3=0.      $ 'Total elimination clearance of Cr(III)'
                        'from blood (L/da/kg)'
QE3=QEC3*WADULT**.74
                        'Total elimination clearance of Cr(III)'
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                        'from blood in the adult (L/da)'
CONSTANT QEC6=0.     $ 'Total elimination clearance of Cr(VI)'
                        'from blood (L/da/kg)'
QE6=QEC6*WADULT**.74
                        'Total elimination clearance of Cr(VI)'
                        'from blood in the adult (L/da)'

CONSTANT CR=50.      $ 'Fractional deposition of chromium from blood'
                        'into forming bone'


'**Exposure Definition**'
CONSTANT BEGIN=0.    $ 'Age at beginning of controlled exposure (da)'
CONSTANT END=0.      $ 'Age at end of controlled exposure (da)'

CONSTANT WATER3=0.   $ 'Concentration of Cr(III) in drinking'
                        'water (mg/L)'
CONSTANT WATER6=0.   $ 'Concentration of Cr(VI) in drinking'
                        'water (mg/L)'
CONSTANT RDRINK=.03  $ 'Rate of drinking water consumption in the'
                        'adult rat (L/da)'
INGST3=WATER3*RDRINK
                        'Rate of ingestion of Cr(III) in the adult'
                        'rat (mg/da)'
INGST6=WATER6*RDRINK
                        'Rate of ingestion of Cr(VI) in the adult'
                        'rat (mg/da)'
CONSTANT KGI3=0.     $ 'First-order rate constant for absorption of'
                        'Cr(III) from GI tract'
CONSTANT KGI6=0.     $ 'First-order rate constant for absorption of'
                        'Cr(VI) from GI tract'

CONSTANT AIR3=0.     $ 'Concentration of Cr(III) in air of exposure'
                        'chamber (mg/m3)'
CONSTANT AIR6=0.     $ 'Concentration of Cr(VI) in air of exposure'
                        'chamber (mg/m3)'
CONSTANT RESPC=.515  $ 'Respiration rate in the 1-kg animal (m3/da/kg)'
RESP=RESPC*(WADULT**.74)
                        'Respiration rate in the adult rat (m3/da)'
INHAL3=RESP*AIR3     $ 'Rate of inhalation of Cr(III) in the adult'
                        'rat (mg/da)'
INHAL6=RESP*AIR6     $ 'Rate of inhalation of Cr(VI) in the adult'
                        'rat (mg/da)'
CONSTANT DEP3=.5     $ 'Fraction of inhaled Cr(III) deposited in the'
                        'lung'
CONSTANT DEP6=.5     $ 'Fraction of inhaled Cr(VI) deposited in the'
                        'lung'
CONSTANT KLU3=0.     $ 'First-order rate constant for absorption of'
                        'Cr(III) from the lung'
CONSTANT KLU6=0.     $ 'First-order rate constant for absorption of'
                        'Cr(VI) from the lung'
CONSTANT KMUCO=.035  $ 'First-order rate constant for mucociliary'
                        'clearance of chromium from the lung (1/da)'
CONSTANT KFX=2.      $ 'First-order rate constant for passage of'
                        'chromium out of the intestine and into'
                        'the feces (1/da)'

CONSTANT DOSE3=0.    $ 'Intravenous Cr(III) dose (mg)'
CONSTANT DOSE6=0.    $ 'Intravenous Cr(VI) dose (mg)'
DOSE=DOSE3+DOSE6     $ 'Total intravenous chromium dose (mg)'

CONSTANT IT3=0.      $ 'Intratracheal Cr(III) dose (mg)'
```

```
CONSTANT IT6=0.      $ 'Intratracheal Cr(VI) dose (mg)'
IT=IT3+IT6           $ 'Total intratracheal chromium dose (mg)'

'**Setup for Data Plotting**'
INTEGER I,J                    $ 'Counters for data'
ARRAY XDATA(100),BDAT(100)     $ 'Arrays to hold data'
ARRAY LDAT(100),KDAT(100)      $ 'Arrays to hold data'
ARRAY GIDAT(100),LUDAT(100)    $ 'Arrays to hold data'
ARRAY BBDAT(100),FDAT(100)     $ 'Arrays to hold data'
ARRAY UDAT(100)                $ 'Array to hold data'
CONSTANT PTS=0                 $ 'Total number of data points'
CONSTANT XDATA=100*1.E6        $ 'Used if no actual data'
CONSTANT BDAT=100*1.E-10       $ 'Used if no actual data'
CONSTANT LDAT=100*1.E-10       $ 'Used if no actual data'
CONSTANT KDAT=100*1.E-10       $ 'Used if no actual data'
CONSTANT GIDAT=100*1.E-10      $ 'Used if no actual data'
CONSTANT LUDAT=100*1.E-10      $ 'Used if no actual data'
CONSTANT BBDAT=100*1.E-10      $ 'Used if no actual data'
CONSTANT FDAT=100*1.E-10       $ 'Used if no actual data'
CONSTANT UDAT=100*1.E-10       $ 'Used if no actual data'
I=0                            $ 'Initialize cint counter'
J=1                            $ 'Initialize data counter'


END                  $ 'Of Initial Section'

DYNAMIC

'**Setup for changing communication interval during exposure**'
CINT=STEP(EX)

DERIVATIVE

'**Scaled and Other Derived Parameters**'

AGE=T+AGE0           $ 'Age (da)'
AGEMO=AGE/30.5       $ 'Age (mo)'
WBODYE=.005+WADULT*(EXP(END/30.5)-1.)/(HALF+(EXP(END/30.5)-1.))...
      +CONST*(END/30.5)


PROCEDURAL(WBODY=1,1)
IF (AGEMO.EQ.0.) GOTO ZERO
GOTO NEXT
NEXT..CONTINUE
      WBODY=.005+WADULT*(EXP(AGEMO)-1.)/(HALF+(EXP(AGEMO)-1.))...
      +CONST*AGEMO
                     'Body weight as a function of age (kg)'
GOTO LEAVE
ZERO..CONTINUE
      WBODY=.005   $ 'Body weight at birth (kg)'
GOTO LEAVE
LEAVE..CONTINUE
END


PROCEDURAL(EX=1,1)
IF (AGE.GE.BEGIN.AND.AGE.LE.END) GOTO ON
GOTO OFF
OFF..CONTINUE
      EX=1
GOTO OVER
```

```
ON..CONTINUE
      EX=2
GOTO OVER
OVER..CONTINUE
END


WSKEL=.0606*WBODY**.947
                        'Body weight dependence of skeletal'
                        'weight (kg)'
VBONE=.0194*WBODY**.9445
                        'Volume of bone (L)'
VBONE0=.0289*WBODY0**1.02
                        'Volume of bone at start of simulation (L)'
WBONE=.03983*WBODY**.9942
                    'Weight of bone (kg)'
DBONE=WBONE/VBONE    $ 'Bone density (g/cm3)'
CABONE=.0128*WBODY**1.27
                        'Bone calcium (kg)'

VS=EXCH*VBONE        $ 'Volume of surface exchange compartment'
                        'of bone (L)'

QCG=RSW(WBODY.LE.WADULT,QC*((WBODY/WADULT)**.67),QC)
                        'Cardiac blood output (L/da)'

QEG3=RSW(WBODY.LE.WADULT,QE3*((WBODY/WADULT)**.67),QE3)
                        'Total clearance of Cr(III) from blood (L/da)'
QEB3=.3*QEG3         $ 'Biliary clearance of Cr(III) (L/da)'
QEU3=.8*(QEG3-QEB3)  $ 'Urinary clearance of Cr(III) (L/da)'
QEI3=.2*(QEG3-QEB3)  $ 'Clearance of Cr(III) from GI tract (L/da)'

QEG6=RSW(WBODY.LE.WADULT,QE6*((WBODY/WADULT)**.67),QE6)
                        'Total clearance of Cr(VI) from blood (L/da)'
QEB6=.05*QEG6        $ 'Biliary clearance of Cr(VI) (L/da)'
QEU6=.8*(QEG6-QEB6)  $ 'Urinary clearance of Cr(VI) (L/da)'
QEI6=.2*(QEG6-QEB6)  $ 'Clearance of Cr(VI) from GI tract (L/da)'

QL=QLC*QCG           $ 'Blood flow to liver (L/da)'
QK=QKC*QCG           $ 'Blood flow to kidney (L/da)'
QI=QIC*QCG           $ 'Blood flow to GI tract (L/da)'
QW=QWC*QCG           $ 'Blood flow to other well-perfused'
                        'tissues (L/da)'
QB=QBC*QCG           $ 'Blood flow to bone (L/da)'
QP=QPC*QCG           $ 'Blood flow to other poorly-perfused'
                        'tissues (L/da)'

VL=VLC*WADULT*((WBODY/WADULT)**.73)
                        'Liver volume (L)'
VK=VKC*WADULT*((WBODY/WADULT)**.67)
                        'Kidney volume (L)'
VI=VIC*WADULT*((WBODY/WADULT)**.7)
                        'Volume of GI tract (L)'
VWT=VWC*WADULT*((WBODY/WADULT)**.7)
                        'Total volume of well-perfused tissues (L)'
VW=VWT-VL-VK-VI      $ 'Volume of other well-perfused tissues (L)'
VP=WBODY-VBONE-VWT   $ 'Volume of other poorly-perfused tissues (L)'


'**Condition for Termination of Run**'
TERMT(T.GE.TSTOP)
```

```
'**KINETICS**'
RWBODY=(((WADULT*HALF*EXP(AGEMO))/(HALF+(EXP(AGEMO)-1.))**2.)...
      +CONST)/30.5 $'Rate of change of body weight (kg/da)'
RWBONE=.9942*.03983*(WBODY**(-.0058))*RWBODY
                        'Rate of change of bone weight (kg/da)'
RVBONE=.9445*.0194*(WBODY**(-.0555))*RWBODY
                        'Rate of change of bone volume (L/da)'
RCBONE=1.27*.0128*(WBODY**.27)*RWBODY
                        'Rate of change of calcium content of'
                        'bone (kg/da)'
FCAAR=RCBONE/CABONE $ 'Fractional calcium accretion rate (1/da)'
FBW=RWBONE/WBONE    $ 'Fractional rate of change of bone'
                        'weight (1/da)'
FBFR=MINFOR+ALPHA0*EXP(-ALPHA*AGE)+BETA0*EXP(-BETA*AGE)
                        'Fractional bone formation rate (by volume)'
                        '(1/da)'
BFR=FBFR*VBONE      $ 'Bone formation rate (L/da)'
BRR=BFR-RVBONE      $ 'Bone resorption rate (L/da)'
FBRR=BRR/VBONE      $ 'Fractional bone resorption rate (by volume)'
                        '(1/da)'

'**Balances**'
FLOW=QCG-(QL+QK+QI+QW+QP+QB)
VOLUME=WBODY-(VL+VK+VI+VW+VP+VBONE)

BURDEN=AL+AK+AI+AP+AW+AB
                        'Body burden of chromium (mg)'
PCENT=RSW(DOSE.EQ.0.,0.,100.*(BURDEN+AGI+ALU)/(DOSE+1.E-33))
                        'Body burden as a percent of IV dose'
MASS=AGIT3+AGIT6+ALUN3+ALUN6+AIT3+AIT6-(BURDEN+AGI+ALU+AX)
WEBBB=RSW(IT.EQ.0.,0.,100.*(BURDEN+AGI+ALU)/(IT+1.E-33))
                        'Percent intratracheal dose remaining in body,'
                        'as data were reported by Weber (1983)'

'**Absorption of Chromium**'
GI3=RSW((AGE.GE.BEGIN).AND.(AGE.LE.END),INGST3,0.)
                        'On-off switch for oral Cr(III) exposure (mg/da)'
GI6=RSW((AGE.GE.BEGIN).AND.(AGE.LE.END),INGST6,0.)
                        'On-off switch for oral Cr(VI) exposure (mg/da)'
RREDGI=KREDGI*AGI6  $ 'Rate of reduction of Cr(VI) to Cr(III)'
                        'in GI tract contents (mg/da)'
RAFX3=KFX*AGI3      $ 'Rate of passage of Cr(III) out of the intestine'
                        'into the feces (mg/da)'
RAFX6=KFX*AGI6      $ 'Rate of passage of Cr(VI) out of the intestine'
                        'into the feces (mg/da)'

RAGIT3=GI3*((WBODY/WADULT)**.67)
                        'Rate of entry of Cr(III) into GI tract from'
                        'drinking water (mg/da)'
AGIT3=INTEG(RAGIT3,0.)
                        'Total amount of Cr(III) that has entered GI'
                        'tract from drinking water (mg)'
RAGI3=RAGIT3+RMUCO3+RREDGI+RAIX3+RALX3-RAFX3-KGI3*AGI3
                        'Rate of change of amount of Cr(III) in GI tract'
                        'contents (mg/da)'
AGI3=INTEG(RAGI3,0.)
                        'Amount of Cr(III) in GI tract contents (mg)'

RAGIT6=GI6*((WBODY/WADULT)**.67)
                        'Rate of entry of Cr(VI) into GI tract from'
                        'drinking water (mg/da)'
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AGIT6=INTEG(RAGIT6,0.)
                        'Total amount of Cr(VI) that has entered GI'
                        'tract from drinking water (mg)'
RAGI6=RAGIT6+RMUCO6-RREDGI+RAIX6+RALX6-RAFX6-KGI6*AGI6
                        'Rate of change of amount of Cr(VI) in GI tract'
                        'contents (mg/da)'
AGI6=INTEG(RAGI6,0.)
                        'Amount of Cr(VI) in GI tract contents (mg)'

RAGI=RAGI3+RAGI6     $ 'Total rate of change of amount of chromium in'
                        'GI tract contents (mg/da)'
AGI=AGI3+AGI6        $ 'Total amount of chromium in GI tract'
                        'contents (mg)'

ITDOSE=RSW(AGE.GE.BEGIN.AND.AGE.LE.END,AGE-BEGIN,0.)
                        'Time since administration of IT dose (da)'
RAIT3=RSW(AGE.GE.BEGIN.AND.AGE.LE.END,100.*IT3*EXP(-100.*ITDOSE),0.)
                        'Rate of entry of IT dose of Cr(III) into the'
                        'absorbable fraction in the lung (mg/da)'
AIT3=INTEG(RAIT3,0.)$   'Amount of IT dose of Cr(III) entering the'
                        'absorbable fraction in the lung (mg)'
RAIT6=RSW(AGE.GE.BEGIN.AND.AGE.LE.END,100.*IT6*EXP(-100.*ITDOSE),0.)
                        'Rate of uptake of IT dose of Cr(VI) into the'
                        'absorbable fraction in the lung (mg/da)'
AIT6=INTEG(RAIT6,0.)$   'Amount of IT dose of Cr(VI) entering the'
                        'absorbable fraction in the lung (mg)'
AIT=AIT3+AIT6        $ 'Total amount of chromium entering the'
                        'absorbable fraction in the lung (mg)'

LU3=RSW((AGE.GE.BEGIN).AND.(AGE.LE.END),INHAL3,0.)
                        'On-off switch for exposure to Cr(III)'
                        'by inhalation (mg/da)'
LU6=RSW((AGE.GE.BEGIN).AND.(AGE.LE.END),INHAL6,0.)
                        'On-off switch for exposure to Cr(VI)'
                        'by inhalation (mg/da)'
RMUCO3=KMUCO*ALU3    $ 'Rate of removal of Cr(III) from the lung to'
                        'the GI tract by mucociliary clearance (mg/da)'
RMUCO6=KMUCO*ALU6    $ 'Rate of removal of Cr(VI) from the lung to'
                        'the GI tract by mucociliary clearance (mg/da)'
RMUCO=RMUCO3+RMUCO6  $ 'Total rate of removal of chromium from the lung'
                        'to the GI tract by mucociliary clearance (mg/da)'

RREDLU=KRED*ALU6     $ 'Rate of reduction of Cr(VI) to Cr(III) (mg/da)'

RALUN3=DEP3*LU3*((WBODY/WADULT)**.67)
                        'Rate of deposition of Cr(III) in the lung'
                        'during inhalation exposure (mg/da)'
ALUN3=INTEG(RALUN3,0.)
                        'Total amount of Cr(III) deposited in the lung'
                        'during inhalation exposure (mg)'
RALU3=DEP3*LU3*((WBODY/WADULT)**.67)-KMUCO*ALU3+RREDLU-KLU3*ALU3...
      +RAIT3
                        'Rate of change of amount of Cr(III) available'
                        'for absorption from the lung (mg/da)'
ALU3=LIMINT(RALU3,0.,0.,1000.)
                        'Amount of Cr(III) available for absorption from'
                        'the lung (mg)'

RALUN6=DEP6*LU6*((WBODY/WADULT)**.67)
                        'Rate of deposition of Cr(VI) in the lung'
                        'during inhalation exposure (mg/da)'
ALUN6=INTEG(RALUN6,0.)
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                        'Total amount of Cr(VI) deposited in the lung'
                        'during inhalation exposure (mg)'
RALU6=DEP6*LU6*((WBODY/WADULT)**.67)-KMUCO*ALU6-RREDLU-KLU6*ALU6...
      +RAIT6
                        'Rate of change of amount of Cr(VI) available'
                        'for absorption from the lung (mg/da)'
ALU6=LIMINT(RALU6,0.,0.,1000.)
                        'Amount of Cr(VI) available for absorption from'
                        'the lung (mg)'

ALU=ALU3+ALU6         $ 'Total amount of chromium in the lung (mg)'
WEBLU=RSW(IT.EQ.0.,0.,100.*ALU/(IT+1.E-33))
                        'Percent intratracheal dose found in lung,'
                        'as data were reported by Weber (1983)'

TDOSE=RSW(AGE.GE.BEGIN.AND.AGE.LE.END,AGE-BEGIN,0.)
                        'Time since injection of IV dose (da)'
RAIV3=RSW(AGE.GE.BEGIN.AND.AGE.LE.END,100.*DOSE3*EXP(-100.*TDOSE),0.)
                        'Rate of uptake of IV dose of Cr(III) (mg/da)'
AIV3=INTEG(RAIV3,0.)
                        'Amount of IV dose of Cr(III) taken up (mg)'
RAIV6=RSW(AGE.GE.BEGIN.AND.AGE.LE.END,100.*DOSE6*EXP(-100.*TDOSE),0.)
                        'Rate of uptake of IV dose of Cr(VI) (mg/da)'
AIV6=INTEG(RAIV6,0.)
                        'Amount of IV dose of Cr(VI) taken up (mg)'

RAIV=RAIV3+RAIV6      $ 'Total rate of uptake of IV chromium (mg/da)'
AIV=AIV3+AIV6         $ 'Total amount of IV chromium taken up (mg)'


'**Chromium in the Red Cell**'
RCRBC6=KIN6*CBPA6-(KRED+KOUT)*CRBC6
                        'Rate of change of concentration of Cr(VI) in'
                        'the red cell (mg/da)'
CRBC6=LIMINT(RCRBC6,0.,0.,1000.)
                        'Concentration of Cr(VI) in the red cell (mg/L)'
RCRBC3=KRED*CRBC6-KOUT*CRBC3
                        'Rate of change of concentration of Cr(III) in'
                        'the red cell (mg/da)'
CRBC3=INTEG(RCRBC3,0.)
                        'Concentration of Cr(III) in the red cell (mg/L)'
CRBC=CRBC6+CRBC3      $ 'Total concentration of chromium in the'
                        'red cell (mg/L)'


'**Chromium in Blood**'
CBV3=RSW(T.EQ.0.,0.,(QL*CBL3+QK*CBK3+QI*CBI3+QW*CBW3+QP*CBP3+...
      QB*CBH3+RAIV3)/QCG)
                        'Concentration of Cr(III) in venous blood (mg/L)'
CBPV3=CBV3/.55        $ 'Concentration of Cr(III) in venous plasma,'
                        'assuming that all Cr(III) is in plasma (mg/L)'
CBA3=(WDOUT*(CL3+CI3+CW3)+KDOUT*CK3+PDOUT*CP3+BDOUT*CS3*(1.-RVAF/QB)+...
      KLU3*ALU3+RARB3+RAIV3+KOUT*CRBC3)/(4.*WDIN+PDIN+BDIN+RVAF*...
      (1.-BDIN/QB))
                        'Concentration of Cr(III) in arterial'
                        'blood (mg/L)'
CBPA3=(CBA3-.45*CRBC3)/.55
                        'Concentration of Cr(III) in arterial plasma'
                        '(mg/L)'

CBPV6=RSW(T.EQ.0.,0.,(QL*CBPL6+QK*CBPK6+QI*CBPI6+QW*CBPW6+QP*CBPP6+...
      QB*CBPH6+RAIV6)/QCG)
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                        'Concentration of Cr(VI) in venous plasma (mg/L)'
CBV6=.55*CBPV6+.45*CRBC6
                        'Concentration of Cr(VI) in venous blood (mg/L)'
CBPA6=(QL*CL6+QK*CK6+QI*CI6+QW*CW6+QP*CP6+QB*CS6*(1.-RVAF/QB)...
      +RARB6+RAIV6+KLU6*ALU6+KOUT*CRBC6)/(QCG+KIN6)
                        'Concentration of Cr(VI) in arterial plasma'
                        '(mg/L)'
CBA6=.55*CBPA6+.45*CRBC6
                        'Concentration of Cr(VI) in arterial blood'
                        '(mg/L)'

CBV=CBV3+CBV6         $ 'Total concentration of chromium in venous'
                        'blood (mg/L)'
CBA=CBA3+CBA6         $ 'Total concentration of chromium in arterial'
                        'blood (mg/L)'


'**Excretion of Chromium in Urine**'
RAKX3=QEU3*CBA3       $ 'Rate of excretion of Cr(III) (mg/da)'
AKX3=INTEG(RAKX3,0.)
                        'Cumulative amount of Cr(III) excreted (mg)'

RAKX6=QEU6*CBK6       $ 'Rate of excretion of Cr(VI) (mg/da)'
AKX6=INTEG(RAKX6,0.)
                        'Cumulative amount of Cr(VI) excreted (mg)'

RAKX=RAKX3+RAKX6      $ 'Total rate of excretion of chromium in'
                        'urine (mg/da)'
AKX=AKX3+AKX6         $ 'Total amount of chromium excreted in'
                        'urine (mg)'
PCENTU=RSW(DOSE.EQ.0.,0.,100.*AKX/(DOSE+1.E-33))
                        'Percent intravenous dose found in urine'


'**Excretion of Chromium in Bile**'
RALX3=QEB3*CBA3       $ 'Rate of excretion of Cr(III) (mg/da)'
ALX3=INTEG(RALX3,0.)
                        'Cumulative amount of Cr(III) excreted (mg)'

RALX6=QEB6*CBL6       $ 'Rate of excretion of Cr(VI) (mg/da)'
ALX6=INTEG(RALX6,0.)
                        'Cumulative amount of Cr(VI) excreted (mg)'
RALX=RALX3+RALX6      $ 'Total rate of excretion of chromium in'
                        'bile (mg/da)'
ALX=ALX3+ALX6         $ 'Total amount of chromium excreted in'
                        'bile (mg)'


'**Excretion of Chromium across Intestine**'
RAIX3=QEI3*CBA3       $ 'Rate of excretion of Cr(III) (mg/da)'
AIX3=INTEG(RAIX3,0.)
                        'Cumulative amount of Cr(III) excreted (mg)'

RAIX6=QEI6*CBI6       $ 'Rate of excretion of Cr(VI) (mg/da)'
AIX6=INTEG(RAIX6,0.)
                        'Cumulative amount of Cr(VI) excreted (mg)'

RAIX=RAIX3+RAIX6      $ 'Total rate of excretion of chromium across'
                        'intestine (mg/da)'
AIX=AIX3+AIX6         $ 'Total amount of chromium excreted across'
                        'intestine (mg)'
```

```
AK3=INTEG(RAK3,0.)   $ 'Amount of Cr(III) (mg)'
CK3=AK3/VK           $ 'Concentration of Cr(III) (mg/L)'
CBK3=CBA3-(WDIN*CBA3-KDOUT*CK3)/QK
                       'Concentration of Cr(III) in venous blood'
                       'leaving kidney (mg/L)'
CBPK3=CBK3/.55

RAK6=QK*(CBA6-CBK6)-RAKX6-RREDK
                       'Rate of change of Cr(VI) (mg/da)'
AK6=INTEG(RAK6,0.)   $ 'Amount of Cr(VI) (mg)'
CK6=AK6/VK           $ 'Concentration of Cr(VI) (mg/L)'
CBPK6=AK6/VK         $ 'Concentration of Cr(VI) in venous plasma'
                       'leaving kidney (mg/L)'
CBK6=.55*CBPK6+.45*CRBC6
                       'Concentration of Cr(VI) in venous blood'
                       'leaving kidney (mg/L)'

RREDK=KRED*AK6       $ 'Rate of reduction of Cr(VI) to Cr(III) (mg/da)'
AK=AK3+AK6           $ 'Total amount of chromium in kidney (mg)'
CK=AK/VK             $ 'Total concentration in kidney (mg/L)'
PCENTK=RSW(DOSE.EQ.0.,0.,100.*AK/(DOSE+1.E-33))
                       'Percent intravenous dose found in kidney'
VISEKK=.001*PCENTK/VK
                       'Percent intravenous dose per g of kidney,'
                       'as data were reported by Visek et al. (1953)'
WEBK=RSW(IT.EQ.0.,0.,100.*AK/(IT+1.E-33))
                       'Percent intratracheal dose found in kidney,'
                       'as data were reported by Weber (1983)'

'**Chromium in GI Tract**'
RAI3=WDIN*CBA3-WDOUT*CI3-RAIX3+RREDI
                       'Rate of change of Cr(III) (mg/da)'
AI3=INTEG(RAI3,0.)   $ 'Amount of Cr(III) (mg)'
CI3=AI3/VI           $ 'Concentration of Cr(III) (mg/L)'
CBI3=CBA3-(WDIN*CBA3-WDOUT*CI3)/QI
                       'Concentration of Cr(III) in venous blood'
                       'leaving the GI tract (mg/L)'
CBPI3=CBI3/.55

RAI6=QI*(CBA6-CBI6)-RAIX6-RREDI
                       'Rate of change of Cr(VI) (mg/da)'
AI6=INTEG(RAI6,0.)   $ 'Amount of Cr(VI) (mg)'
CI6=AI6/VI           $ 'Concentration of Cr(VI) (mg/L)'
CBPI6=AI6/VI         $ 'Concentration of Cr(VI) in venous plasma'
                       'leaving the GI tract (mg/L)'
CBI6=.55*CBPI6+.45*CRBC6
                       'Concentration of Cr(VI) in venous blood'
                       'leaving the GI tract (mg/L)'

RREDI=KRED*AI6       $ 'Rate of reduction of Cr(VI) to Cr(III) (mg/da)'
AI=AI3+AI6           $ 'Total amount of chromium in GI tract (mg)'
CI=AI/VI             $ 'Total concentration in GI tract (mg/L)'
PCENTI=RSW(DOSE.EQ.0.,0.,100.*AI/(DOSE+1.E-33))
                       'Percent intravenous dose found in GI tract'
WEBI=RSW(IT.EQ.0.,0.,100.*AI/(IT+1.E-33))
                       'Percent intratracheal dose found in GI tract,'
                       'as data were reported by Weber (1983)'

'**Chromium in Other Well-Perfused Tissues**'
RAW3=WDIN*CBA3-WDOUT*CW3+RREDW
                       'Rate of change of Cr(III) (mg/da)'
AW3=INTEG(RAW3,0.)   $ 'Amount of Cr(III) (mg)'
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CW3=AW3/VW          $ 'Concentration of Cr(III) (mg/L)'
CBW3=CBA3-(WDIN*CBA3-WDOUT*CW3)/QW
                      'Concentration of Cr(III) in venous blood'
                      'leaving other well-perfused tissues (mg/L)'
CBPW3=CBW3/.55

RAW6=QW*(CBA6-CBW6)-RREDW
                      'Rate of change of Cr(VI) (mg/da)'
AW6=INTEG(RAW6,0.)  $ 'Amount of Cr(VI) (mg)'
CW6=AW6/VW          $ 'Concentration of Cr(VI) (mg/L)'
CBPW6=AW6/VW        $ 'Concentration of Cr(VI) in venous plasma'
                      'leaving other well-perfused tissues (mg/L)'
CBW6=.55*CBPW6+.45*CRBC6
                      'Concentration of Cr(VI) in venous blood'
                      'leaving other well-perfused tissues (mg/L)'

RREDW=KRED*AW6      $ 'Rate of reduction of Cr(VI) to Cr(III) (mg/da)'
AW=AW3+AW6          $ 'Total amount of chromium in other well-'
                      'perfused tissues (mg)'
CW=AW/VW            $ 'Total concentration in other well-perfused'
                      'tissues (mg/L)'
PCENTW=RSW(DOSE.EQ.0.,0.,100.*AW/(DOSE+1.E-33))
                      'Percent intravenous dose found in other well-'
                      'perfused tissues'


'**Chromium in Poorly-Perfused Tissues**'
RAP3=PDIN*CBA3-PDOUT*CP3+RREDP
                      'Rate of change of Cr(III) (mg/da)'
AP3=INTEG(RAP3,0.)  $ 'Amount of Cr(III) (mg)'
CP3=AP3/(VP-VBONE)  $ 'Concentration of Cr(III) (mg/L)'
CBP3=CBA3-(PDIN*CBA3-PDOUT*CP3)/QP
                      'Concentration of Cr(III) in venous blood'
                      'leaving poorly-perfused tissues (mg/L)'
CBPP3=CBP3/.55

RAP6=QP*(CBA6-CBP6)-RREDP
                      'Rate of change of Cr(VI) (mg/da)'
AP6=INTEG(RAP6,0.)  $ 'Amount of Cr(VI) (mg)'
CP6=AP6/(VP-VBONE)  $ 'Concentration of Cr(VI) (mg/L)'
CBPP6=AP6/(VP-VBONE)$ 'Concentration of Cr(VI) in venous plasma'
                      'leaving poorly-perfused tissues (mg/L)'
CBP6=.55*CBPP6+.45*CRBC6
                      'Concentration of Cr(VI) in venous blood'
                      'leaving poorly-perfused tissues (mg/L)'

RREDP=KRED*AP6      $ 'Rate of reduction of Cr(VI) to Cr(III) (mg/da)'
AP=AP3+AP6          $ 'Total amount of chromium in poorly-'
                      'perfused tissues (mg)'
CP=AP/(VP-VBONE)    $ 'Total concentration in poorly-perfused'
                      'tissues (mg/L)'
PCENTP=RSW(DOSE.EQ.0.,0.,100.*AP/(DOSE+1.E-33))
                      'Percent intravenous dose found in other poorly-'
                      'perfused tissues'


'**Chromium in Surface Bone**'
CONSTANT BDINC=.08
BDIN=BDINC*(WADULT**.74)
CONSTANT BDOUTC=.08
BDOUT=BDOUTC*(WADULT**.74)
RAS3=BDIN*CBA3-BDOUT*CS3
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                          'Rate of surface exchange of Cr(III) (mg/da)'
AS3=INTEG(RAS3,0.)     $ 'Amount of Cr(III) incorporated by surface'
                          'exchange (mg)'
CS3=AS3/VS             $ 'Concentration of Cr(III) in the surface'
                          'exchange region (mg/L)'
CBS3=CBA3-(BDIN*CBA3-BDOUT*CS3)/QB
                          'Concentration of Cr(III) in venous blood'
                          'leaving the surface exchange region (mg/L)'
CBPS3=CBS3/.55

RAS6=QB*(CBA6-CBS6)    $ 'Rate of surface exchange of Cr(VI) (mg/da)'
AS6=INTEG(RAS6,0.)     $ 'Amount of Cr(VI) incorporated by surface'
                          'exchange (mg)'
CS6=AS6/VS             $ 'Concentration of Cr(VI) in the surface'
                          'exchange region (mg/L)'
CBPS6=AS6/VS           $ 'Concentration of Cr(VI) in venous plasma'
                          'leaving the surface exchange region (mg/L)'
CBS6=.55*CBPS6+.45*CRBC6
                          'Concentration of Cr(VI) in venous blood'
                          'leaving the surface exchange region (mg/L)'

AS=AS3+AS6             $ 'Total amount of chromium in the surface'
                          'exchange region of bone (mg)'
CS=AS/VS               $ 'Total concentration in the surface exchange'
                          'region of bone (mg/L)'


'**Chromium in Metabolically Active Region of Bone**'
RVAF=CR*BFR            $ 'Clearance of chromium from blood during'
                          'mineralization of newly-apposed bone (L/da)'
RAFB3=RVAF*CBPS3       $ 'Rate of deposition of Cr(III) with new bone'
                          'in the metabolically active region of bone'
                          '(mg/da)'
RARB3=BRR*CB3          $ 'Rate of return of Cr(III) to blood with'
                          'resorption of bone (mg/da)'
RABH3=RAFB3-RARB3      $ 'Rate of accumulation of Cr(III) in the'
                          'metabolic region of bone (mg/da)'
ABH3=INTEG(RABH3,0.)$ 'Amount of Cr(III) in the metabolic region'
                          'of bone (mg)'

RAMB3=RARB3-RAFB3      $ 'Net rate of change of amount of Cr(III) in'
                          'plasma perfusing the metabolic region of bone'
                          '(mg/da)'
CBH3=RSW((T.EQ.0.),0.,(CBPS3+RAMB3/QB))
                          'Concentration of Cr(III) in blood leaving the'
                          'metabolically active region of bone (mg/L)'
CBPH3=CBH3/.55         $ 'Concentration of Cr(III) in plasma leaving the'
                          'metabolically active region of bone (mg/L)'

AB3=AS3+ABH3           $ 'Total amount of Cr(III) in bone (mg)'
CB3=AB3/VBONE          $ 'Total bone Cr(III) concentration (mg/L)'
CSKEL3=CB3*VBONE/WSKEL
                          'Total skeletal Cr(III) concentration (ug/g)'

RAFB6=RVAF*CBPS6       $ 'Rate of deposition of Cr(VI) with new bone'
                          'in the metabolically active region of bone'
                          '(mg/da)'
RARB6=BRR*CB6          $ 'Rate of return of Cr(VI) to blood with'
                          'resorption of bone (mg/da)'
RABH6=RAFB6-RARB6      $ 'Rate of accumulation of Cr(VI) in the'
                          'metabolic region of bone (mg/da)'
ABH6=INTEG(RABH6.0.)$ 'Amount of Cr(VI) in the metabolic region'
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                        'of bone (mg)'

RAMB6=RARB6-RAFB6    $ 'Net rate of change of amount of Cr(VI) in'
                        'blood perfusing the metabolic region of bone'
                        '(mg/da)'
CBPH6=RSW((T.EQ.0.),0.,(CBPS6+RAMB6/QB))
                        'Concentration of Cr(VI) in plasma leaving the'
                        'metabolically active region of bone (mg/L)'
CBH6=.55*CBPH6+.45*CRBC6
                        'Concentration of Cr(VI) in blood leaving the'
                        'metabolically active region of bone (mg/L)'

AB6=AS6+ABH6         $ 'Total amount of Cr(VI) in bone (mg)'
CB6=AB6/VBONE        $ 'Total bone Cr(VI) concentration (mg/L)'
CSKEL6=CB6*VBONE/WSKEL
                        'Total skeletal Cr(VI) concentration (ug/g)'

AB=AB3+AB6           $ 'Total amount of chromium in bone (mg)'
CB=AB/VBONE          $ 'Total concentration in bone (mg/L)'
CSKEL=CB*VBONE/WSKEL
                        'Total concentration in skeleton (ug/g)'
PCENTB=RSW(DOSE.EQ.0.,0.,100.*AB/(DOSE+1.E-33))
VISEKB=.001*PCENTB/WBONE
                        'Percent intravenous dose per g of bone,'
                        'as data were reported by Visek et al. (1953)'


END                  $ 'Of Derivative Section'

'**Add a Point at Each Communication Interval**'
IF (J.GT.PTS)  GOTO DONE
IF (XDATA(J).LE.T)  GOTO CALC1
     GOTO DONE
CALC1..CONTINUE
     TDATA=AGE
     BDATA=BDAT(J)
     LDATA=LDAT(J)
     KDATA=KDAT(J)
     GIDATA=GIDAT(J)
     LUDATA=LUDAT(J)
     BBDATA=BBDAT(J)
     UDATA=UDAT(J)
     FDATA=FDAT(J)
     J=J+1
     I=I+1
GOTO OUT
DONE..CONTINUE
     TDATA=1.E6
     BDATA=1.E-10
     LDATA=1.E-10
     KDATA=1.E-10
     GIDATA=1.E-10
     LUDATA=1.E-10
     BBDATA=1.E-10
     UDATA=1.E-10
     FDATA=1.E-10
     I=I+1
OUT..CONTINUE
END
```

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END
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CHROMIUM.CMD file follows:

```
SET TITLE = 'RAT PBTK MODEL: CHROMIUM'

PREPAR AGE,T,TSTOP,CINT,AGE0,BEGIN,END,TDOSE,MASS,BURDEN
PREPAR VBONE0,PCENT,PCENTL,PCENTK,PCENTI,PCENTW,PCENTP,PCENTB
PREPAR WADULT,HALF,WBODY,WBODY0,WSKEL,WBONE,VBONE,DBONE
PREPAR QCC,QC,QCG,QLC,QL,QKC,QK,QIC,QI,QWC,QW,QPC,QP,QBC,QB
PREPAR QEC3,QE3,QEG3,QEC6,QE6,QEG6,QEU3,QEI3,QEB3,QEU6,QEI6,QEB6
PREPAR VLC,VL,VKC,VK,VIC,VI,VWC,VW,VPC,VP,VS,ALUN3,ALUN6
PREPAR RREDL,RREDK,RREDI,RREDW,RREDP,RREDGI,RRED,AX,RAFX,RAKX,RAX
PREPAR RAL3,RAL6,RAK3,RAK6,RAI3,RAI6,RAW3,RAW6,RAP3,RAP6,RAS3,RAS6
PREPAR RABH3,RABH6,RAGI3,RAGI6,RAGI,RAIV3,RAIV6,RAIV
PREPAR RAKX3,RAKX6,RALX3,RALX6,RAIX3,RAIX6,RAFX,GI3,GI6,INGST3,INGST6
PREPAR AL3,AL6,AL,AK3,AK6,AK,AI3,AI6,AI,AW3,AW6,AW,AP3,AP6,AP,AS3,AS6,AS
PREPAR AB3,AB6,AB,ALX3,ALX6,ALX,AIX3,AIX6,AIX,AKX3,AKX6,AKX,AFX,ABH3
PREPAR ABH6,FLOW,VOLUME,MASS,BURDEN,RAFB3,RARB3,RAFB6,RARB6
PREPAR CL3,CL6,CL,CK3,CK6,CK,CI3,CI6,CI,CW3,CW6,CW,CP3,CP6,CP,CS3,CS6,CS
PREPAR CBL3,CBL6,CBK3,CBK6,CBI3,CBI6,CBW3,CBW6,CBP3,CBP6,CBS3,CBS6
PREPAR CBH3,CBH6,CB,CBA3,CBA6,CBA,CBV3,CBV6,CBV
PREPAR RWBODY,VBONE,RVBONE,WBONE,RWBONE,DBONE,WSKEL,CABONE,RCBONE
PREPAR FCAAR,FBW,FBFR,FBRR,BFR,BRR,RVAF
PREPAR TDATA,XDATA,CONST,CSKEL,CRBC6,CBPA6,CBPA3,CRBC3
PREPAR RAIV3,RAIV6,AIV3,AIV6,AIV,AGI3,AGI6,AGI,ALU3,ALU6,ALU
PREPAR AGIT3,AGIT6,RAGIT3,RAGIT6,AIT,AIT3,AIT6,RAIT3,RAIT6
PREPAR BDATA,LUDATA,LDATA,GIDATA,KDATA,BBDATA,UDATA,FDATA
PREPAR PCENTU,PCENTF,VISEKL,VISEKK,VISEKB,WEBL,WEBLU,WEBK,WEBBB,WEBI

OUTPUT 'NCIOUT'=10,AGE,CBA


PROCED INITIAL
SET QEC3=.2,QEC6=2.,WDINC=.3,WDOUTC=.012,KDOUTC=.006,KREDGI=2.
SET BDINC=.15,BDOUTC=.0005,PDINC=.1,PDOUTC=.1,KRED=40.
SET KGI3=.002,KGI6=.1,MINFOR=.0035,CR=50.,KLU3=0.,KLU6=40.
SET DEP3=.05,DEP6=.05,KIN6=1.,KOUT=.00045,KMUCO=.035
END


PROCED MALE
SET CONST=.0088,WADULT=.440,HALF=5.,CR=50.,EXCH=.005
END


PROCED FEMALE
SET CONST=0.,WADULT=.250,HALF=5.8,CR=50.,EXCH=.005
END


PROCED TEST3
MALE
SET AGE0=40.,BEGIN=40.,END=80.,TSTOP=40.,STEP=1.,1.,PTS=6.
SET DOSE3=0.,DOSE6=0.,WATER3=12.9,WATER6=0.,AIR3=0.,AIR6=0.
START
END


PROCED TEST6
MALE
SET AGE0=40.,BEGIN=40.,END=80.,TSTOP=40.,STEP=1.,1.,PTS=6.
SET DOSE3=0.,DOSE6=0.,WATER3=0.,WATER6=12.9,AIR3=0.,AIR6=0.
```

```
START
END


PROCED CRIIIIV    $ 'Intravenous injection of Cr(III)'
MALE
SET AGE0=49.,BEGIN=50.,END=100.,TSTOP=4.
SET DOSE3=1.,DOSE6=0.,WATER3=0.,WATER6=0.,AIR3=0.,AIR6=0.
START
END


PROCED MERTZ      $ 'Simulation and plot for conditions of'
                    'Mertz et al, Am. J. Physiol. 209, 489-494 (1965)'
MALE
SET AGE0=29.,BEGIN=30.,END=31.,TSTOP=81.,CR=50.
SET DOSE3=1.,DOSE6=0.,WATER3=0.,WATER6=0.,AIR3=0.,AIR6=0.
START
SET HVDPRN=.F.,XINCPL=4.3,YINCPL=2.24
PLOT 'XAXIS'=AGE,'XLO'=30.,'XHI'=110.,PCENT,'LOG','LO'=10.,'HI'=100.
SET HVDPRN=.T.,XINCPL=6.,YINCPL=4.
END


PROCED PMERTZ
SET HVDPRN=.F.,XINCPL=4.3,YINCPL=2.24
PLOT 'XAXIS'=AGE,'XLO'=30.,'XHI'=110.,PCENT,'LOG','LO'=10.,'HI'=100.
SET HVDPRN=.T.,XINCPL=6.,YINCPL=4.
END


PROCED HOPKINS    $ 'Simulation and plot for conditions of'
                    'Hopkins, Am. J. Physiol. 209, 731-735 (1965)'
MALE
SET AGE0=30.,BEGIN=30.,END=31.,TSTOP=1.,STEP=1.,.01
SET DOSE3=1.,DOSE6=0.,WATER3=0.,WATER6=0.,AIR3=0.,AIR6=0.
OUTPUT 'NCIOUT'=1,T,PCENTB
START
SET AGE0=180.,BEGIN=180.,END=181.,TSTOP=1.,NRWITG=.T.
START
SET HVDPRN=.T.,NRWITG=.F.,STEP=1.,1.
OUTPUT 'NCIOUT'=10,AGE,CBA
END


PROCED CRVIIV     $ 'Intravenous injection of Cr(VI)'
FEMALE
SET AGE0=49.,BEGIN=50.,END=100.,TSTOP=4.
SET DOSE3=0.,DOSE6=1.,WATER3=0.,WATER6=0.,AIR3=0.,AIR6=0.
START
END


PROCED VISEK      $ 'Simulation for conditions of Visek et al,'
                    'PSEBM 84, 610-615 (1983)'
MALE
SET AGE0=260.,BEGIN=260.,END=261.,TSTOP=42.
OUTPUT T,VISEKL,VISEKK,VISEKB,PCENTF,PCENTU
SET DOSE3=0.,DOSE6=1.,WATER3=0.,WATER6=0.,AIR3=0.,AIR6=0.
START
SET DOSE3=1.,DOSE6=0.,WATER3=0.,WATER6=0.,AIR3=0.,AIR6=0.,NRWITG=.T.
START
```

```
SET NRWITG=.F.
OUTPUT 'NCIOUT'=10,AGE,CBA
END


PROCED MACK        $ 'Simulating chronic oral rat study of'
                     'MacKenzie et al, AMA Arch Indust Health'
                     '18, 232-234 (1958)'
MALE
SET AGE0=34.,BEGIN=34.,END=400.,TSTOP=365.,STEP=1.,1.
SET DOSE3=0.,DOSE6=0.,WATER3=0.,WATER6=11.2,AIR3=0.,AIR6=0.
SAVE 'INITIAL'
START
RESTOR 'INITIAL'
SET WATER6=7.7,NRWITG=.T.
START
RESTOR 'INITIAL'
SET WATER6=4.5
START
RESTOR 'INITIAL'
SET WATER6=25.
START
RESTOR 'INITIAL'
SET WATER6=0.,WATER3=25.
START
RESTOR 'INITIAL'
SET NRWITG=.F.
END


PROCED CRIIIGI    $ 'Oral Administration of Cr(III)'
FEMALE
SET AGE0=49.,BEGIN=50.,END=52.,TSTOP=4.
SET DOSE3=0.,DOSE6=0.,WATER3=.5,WATER6=0.,AIR3=0.,AIR6=0.
START
END


PROCED CRVIGI      $ 'Oral Administration of Cr(VI)'
FEMALE
SET AGE0=49.,BEGIN=50.,END=100.,TSTOP=4.
SET DOSE3=0.,DOSE6=0.,WATER3=0.,WATER6=.5,AIR3=0.,AIR6=0.
START
END


PROCED WEBER       $ 'Simulating study of Weber, J. Toxicol.'
                     'Environ. Health 11, 749-764 (1983).'
                     'Chromium given intratracheally.'
MALE
SET AGE0=50.,BEGIN=50.,END=51.,TSTOP=41.,STEP=1.,.1
SET DOSE3=0.,DOSE6=0.,WATER3=0.,WATER6=0.,AIR3=0.,AIR6=0.
SET IT3=0.,IT6=1.,PTS=9.
SET XDATA=.25,1.,2.,3.,6.,10.,15.,25.,40.
SET LDAT=2.6,1.2,1.0,1.0,.84,.79,.58,.39,.31
SET LUDAT=42.9,35.6,31.9,32.7,26.2,27.3,25.7,18.5,12.3
SET KDAT=2.3,2.0,2.0,2.2,2.0,2.2,1.7,.97,.52
SET BBDAT=85.2,53.8,47.,48.5,40.5,41.,37.2,27.1,19.7
SET GIDAT=20.3,1.3,.86,.75,1.0,.54,.51,.41,.26
START
END
```

```
PROCED PWEBER
SET HVDPRN=.F.,DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.,NPCCPL=1
PLOT 'XAXIS'=TDATA,'XLO'=50.,'XHI'=92.,LDATA,'LO'=0.,'HI'=4.
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=T,'XLO'=0.,'XHI'=42.,WEBL,'LO'=0.,'HI'=4.
PAUSE
SET DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.
PLOT 'XAXIS'=TDATA,'XLO'=50.,'XHI'=92.,LUDATA,'LO'=0.,'HI'=60.
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=T,'XLO'=0.,'XHI'=42.,WEBLU,'LO'=0.,'HI'=60.
PAUSE
SET DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.
PLOT 'XAXIS'=TDATA,'XLO'=50.,'XHI'=92.,KDATA,'LO'=0.,'HI'=2.8
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=T,'XLO'=0.,'XHI'=42.,WEBK,'LO'=0.,'HI'=2.8
PAUSE
SET DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.
PLOT 'XAXIS'=TDATA,'XLO'=50.,'XHI'=92.,GIDATA,'LO'=0.,'HI'=24.
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=T,'XLO'=0.,'XHI'=42.,WEBI,'LO'=0.,'HI'=24.
PAUSE
SET DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.
PLOT 'XAXIS'=TDATA,'XLO'=50.,'XHI'=92.,BBDATA,'LO'=0.,'HI'=100.
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=T,'XLO'=0.,'XHI'=42.,WEBBB,'LO'=0.,'HI'=100.
SET HVDPRN=.T.
END


PROCED CRIIILU     $ 'Inhalation of Cr(III)'
FEMALE
SET AGE0=49.,BEGIN=50.,END=100.,TSTOP=4.
SET DOSE3=0.,DOSE6=0.,WATER3=0.,WATER6=0.,AIR3=0.,AIR6=0.
START
END


PROCED CRVILU      $ 'Inhalation of Cr(VI)'
FEMALE
SET AGE0=49.,BEGIN=50.,END=100.,TSTOP=4.
SET DOSE3=0.,DOSE6=0.,WATER3=0.,WATER6=0.,AIR3=0.,AIR6=0.
START
END


PROCED ORALKETT
MALE
SET AGE0=40.,BEGIN=40.,END=80.,TSTOP=70.,STEP=1.,1.,PTS=6.
SET DOSE3=0.,DOSE6=0.,WATER3=0.,WATER6=12.9,AIR3=0.,AIR6=0.
SET XDATA=2.,5.,10.,20.,40.,60.
SET LUDAT=1.E10,1.E10,1.E10,1.17,.65,.45
SET LDAT=.189,.352,.565,1.16,1.48,.489
SET KDAT=.249,.588,1.60,1.71,1.90,.634
SET BDAT=.006,.0088,.0155,.0459,.0553,.0083
SET UDAT=.00062,.00178,.00201,.00308,.00219,.00022
SET FDAT=.156,.140,.143,.155,.242,0.
SAVE 'INITIAL'
START
RESTOR 'INITIAL'
SET WATER6=0.,WATER3=12.9,NRWITG=.T.
SET LUDAT=0.,0.,0.,0.,0.,0.
SET LDAT=0.,0.,0.,0.,0.,0.
```

```
SET KDAT=0.,0.,0.,0.,0.,0.
SET BDAT=0.,.0001,.0138,.0026,.0017,.0025
SET UDAT=.00023,.000065,.000040,.000075,.000017,0.
SET FDAT=.145,.113,.190,.168,.180,0.
START
SET NRWITG=.F.
END


PROCED PORAL
SET HVDPRN=.F.,DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.,NPCCPL=1
PLOT 'XAXIS'=TDATA,'XLO'=40.,'XHI'=120.,BDATA,'LO'=0.,'HI'=.06
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=AGE,'XLO'=40.,'XHI'=120.,CBA,'LO'=0.,'HI'=.06
PAUSE
SET DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.
PLOT 'XAXIS'=TDATA,'XLO'=40.,'XHI'=120.,LDATA,'LO'=0.,'HI'=1.6
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=AGE,'XLO'=40.,'XHI'=120.,CL,'LO'=0.,'HI'=1.6
PAUSE
SET DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.
PLOT 'XAXIS'=TDATA,'XLO'=40.,'XHI'=120.,KDATA,'LO'=0.,'HI'=2.
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=AGE,'XLO'=40.,'XHI'=120.,CK,'LO'=0.,'HI'=2.
PAUSE
SET DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.
PLOT 'XAXIS'=TDATA,'XLO'=40.,'XHI'=120.,UDATA,'LO'=0.,'HI'=.004
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=AGE,'XLO'=40.,'XHI'=120.,RAKX,'LO'=0.,'HI'=.004
PAUSE
SET DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.
PLOT 'XAXIS'=TDATA,'XLO'=40.,'XHI'=120.,FDATA,'LO'=0.,'HI'=.4
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=AGE,'XLO'=40.,'XHI'=120.,RAFX,'LO'=0.,'HI'=.4
SET HVDPRN=.T.
END


PROCED INHKETT
MALE
SET AGE0=40.,BEGIN=40.,END=80.,TSTOP=70.,STEP=1.,.5,PTS=6.
SET DOSE3=0.,DOSE6=0.,WATER3=0.,WATER6=0.,AIR6=.2,AIR3=0.
SET XDATA=2.,5.,10.,20.,40.,60.
SET LUDAT=.00195,.00510,.00753,.0133,.0243,.0130
SET LDAT=0.,.058,.060,.064,.087,.036
SET KDAT=0.,.217,.237,.310,.580,.137
SET BDAT=.0395,.0554,.0708,.0698,.0727,.0368
SET UDAT=.00052,.00021,.00027,.00014,.000047,.000012
SET FDAT=.006,.014,.005,.015,.020,0.
SAVE 'INITIAL'
START
RESTOR 'INITIAL'
SET AIR6=0.,AIR3=.2,STEP=1.,1.,NRWITG=.T.
SET LUDAT=.00343,.00843,.0171,.0354,.0637,.0429
SET LDAT=0.,0.,0.,0.,0.,0.
SET KDAT=0.,0.,0.,0.,0.,0.
SET BDAT=.0585,.0618,.0204,.009,.0596,.086
SET UDAT=.00022,.00010,.000084,.000032,.000002,.000001
SET FDAT=.012,.013,.008,0,.014,.004
START
SET NRWITG=.F.
END
```

```
PROCED PINH
SET HVDPRN=.F.,DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.,NPCCPL=1
PLOT 'XAXIS'=TDATA,'XLO'=40.,'XHI'=120.,BDATA,'LO'=0.,'HI'=.1
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=AGE,'XLO'=40.,'XHI'=120.,CBA,'LO'=0.,'HI'=.1
PAUSE
SET DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.
PLOT 'XAXIS'=TDATA,'XLO'=40.,'XHI'=120.,LUDATA,'LO'=0.,'HI'=.08
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=AGE,'XLO'=40.,'XHI'=120.,ALU,'LO'=0.,'HI'=.08
PAUSE
SET DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.
PLOT 'XAXIS'=TDATA,'XLO'=40.,'XHI'=120.,LDATA,'LO'=0.,'HI'=.1
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=AGE,'XLO'=40.,'XHI'=120.,CL,'LO'=0.,'HI'=.1
PAUSE
SET DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.
PLOT 'XAXIS'=TDATA,'XLO'=40.,'XHI'=120.,KDATA,'LO'=0.,'HI'=.6
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=AGE,'XLO'=40.,'XHI'=120.,CK,'LO'=0.,'HI'=.6
PAUSE
SET DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.
PLOT 'XAXIS'=TDATA,'XLO'=40.,'XHI'=120.,UDATA,'LO'=0.,'HI'=.0006
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=AGE,'XLO'=40.,'XHI'=120.,RAKX,'LO'=0.,'HI'=.0006
PAUSE
SET DEFPLT=.T.,SYMCPL=.T.,LINCPL=.F.
PLOT 'XAXIS'=TDATA,'XLO'=40.,'XHI'=120.,FDATA,'LO'=0.,'HI'=.02
SET SYMCPL=.F.,LINCPL=.T.,DEFPLT=.F.
PLOT 'XAXIS'=AGE,'XLO'=40.,'XHI'=120.,RAFX,'LO'=0.,'HI'=.02
SET HVDPRN=.T.
END


SET HVDPRN=.T.
SET CJVITG=.F.,WESITG=.F.,FTSPLT=.T.,XINCPL=6.,YINCPL=4.,CMD=0
```

APPENDIX C

Tissue Concentrations of CrVI or CrIII at 40 days

Tissue Weight at Autopsy

GROUP	ANIMAL NUMBER	METABOLISM CAGE DATA: FECES IN GRAMS VIAL	SAMPLE	MEAN WETWT	DRYWT	FECES CHROMIUM DATA: FECES ug Cr	FECES ug/wetwt	FECES ug/drywt	MEAN FECES ug/wetwt	FECES MINUSCON ug/wetwt	MEAN FECES MINUSCON ug Cr	MEAN FECES MINUSCON ug Cr/da
C3W	145	13.47	4.88		2.05	136.0	27.86885	66.34146				
C3W	146	13.50	3.88	4.38	1.58	77.3	19.92268	48.92405	23.89576	18.73576	106.65	0.165135
C3W	147											
C3W	148											
C3W	149											
C3W	150											
C3W	151	13.18	3.20		1.55	87.8	27.4375	56.64516				
C3W	152	13.63	2.43	2.815	1.77	84.3	34.69135	47.62711	31.06442	25.90442	86.05	0.133238
C3W	153											
C3W	154											
C3W	155											
C3W	156											
C3W	157	13.59	2.64		1.09	112.0	42.42424	103.2258				
C3W	158	13.17	4.00	3.32	1.71	160.0	40	93.67681	41.21212	36.05212	136	0.210580
C3W	159											
C3W	160											
C3W	161											
C3W	162											
C3W	163	13.56	2.21		1.02	94.8	42.89592	92.94117				
C3W	164	13.59	3.45	2.83	1.34	148.0	42.89855	110.2010	42.89723	37.73723	121.4	0.187974
C3W	165											
C3W	166											
C3W	167											
C3W	168											
C3W	169	13.56	2.22		1.11	80.8	36.39639	72.79279				
C3W	170	13.16	5.17	3.695	2.31	178.0	34.42940	77.05627	35.41289	30.25289	129.4	0.200361
C3W	171											
C3W	172											
C3W	173											
C3W	174											

C3W	175	13.36	4.61		1.77	16.4	3.557483	9.249858				
C3W	176	13.62	1.66	3.135	0.86	7.4	4.457831	8.604651	4.007657	0	11.9	0.018425
C3W	177											
C3W	178											
C3W	179											
C3W	180											
C3I	67	13.41	3.66		1.67	24.0	6.557377	14.37125				
C3I	68	13.52	3.20	3.43	1.44	17.2	5.375	11.94444	5.966188	0.806188	20.6	0.031896
C3I	69											
C3I	70											
C3I	71											
C3I	72											
C3I	37	13.25	3.90		1.81	24.8	6.358974	13.70165				
C3I	38	13.71	3.00	3.45	1.42	18.0	6	12.67605	6.179487	1.019487	21.4	0.033135
C3I	39											
C3I	40											
C3I	41											
C3I	42											
C3I	43	13.61	3.23		1.44	19.0	5.882352	13.22199				
C3I	44	13.48	3.04	3.135	1.43	16.6	5.460526	11.58408	5.671439	0.511439	17.8	0.027561
C3I	45											
C3I	46											
C3I	47											
C3I	48											
C3I	49	13.22	0.38		0.15	3.2	8.421052	20.91503				
C3I	50	13.13	1.83	1.105	0.68	14.0	7.650273	20.55800	8.035662	2.875662	8.6	0.013316
C3I	51											
C3I	52											
C3I	53											
C3I	54											
C3I	55	13.63	2.65		1.15	21.0	7.924528	18.26086				
C3I	56	13.57	3.06	2.855	1.61	23.2	7.581699	14.40993	7.753113	2.593113	22.1	0.034219

C31	57										
C31	58										
C31	59										
C31	60										
C31	61	13.83	4.27		1.81	16.0	3.747072	8.839779			
C31	62	13.42	3.35	3.81	1.72	15.6	4.656716	9.069767	4.201894	0	15.8 0.024464
C31	63										
C31	64										
C31	65										
C31	66										
C61	103	13.47	5.31		1.58	16.4	3.088512	10.37974			
C61	104	13.93	3.18	4.245	1.12	16.6	5.220125	14.82142	4.154319	0	16.5 0.025548
C61	105										
C61	106										
C61	107										
C61	108										
C61	73	13.44	4.43		2.01	21.4	4.830699	10.64676			
C61	74	13.64	4.21	4.32	1.88	23.0	5.463182	12.23404	5.146941	0	22.2 0.034374
C61	75										
C61	76										
C61	77										
C61	78										
C61	79	13.16	3.82		1.60	19.0	4.973821	11.875			
C61	80	13.52	1.93	2.875	0.77	12.8	6.632124	16.71018	5.802973	0.642973	15.9 0.024619
C61	81										
C61	82										
C61	83										
C61	84										
C61	85	13.71	3.06		1.32	21.6	7.058823	16.41337			
C61	86	13.22	3.88	3.47	1.55	23.4	6.030927	15.09677	6.544875	1.384875	22.5 0.034838
C61	87										
C61	88										
C61	89										
C61	90										

C61	91	13.63	2.55		1.28	20.0	7.843137	15.625				
C61	92	13.59	4.35	3.45	2.03	31.4	7.218390	15.46798	7.530764	2.370764	25.7	0.039793
C61	93											
C61	94											
C61	95											
C61	96											
C61	97	13.81	3.46		1.90	14.0	4.046242	7.368421				
C61	98	13.26	3.01	3.235	1.29	12.6	4.186046	9.767441	4.116144	0	13.3	0.020593
C61	99											
C61	100											
C61	101											
C61	102											
C6W	181	13.50	4.27		1.76	147.0	34.42622	83.52272				
C6W	182	13.48	2.07	3.17	0.92	80.3	38.79227	87.28260	36.60925	31.44925	113.65	0.175974
C6W	183											
C6W	184											
C6W	185											
C6W	186											
C6W	187	13.61	3.68		1.80	99.3	26.98369	55.16666				
C6W	188	13.19	4.19	3.935	1.85	108.0	25.77565	58.37837	26.37967	21.21967	103.65	0.160490
C6W	189											
C6W	190											
C6W	191											
C6W	192											
C6W	193	13.54	1.67		0.75	68.8	41.19760	91.85580				
C6W	194	13.14	4.19	2.93	1.44	142.0	33.89021	98.67963	37.54390	32.38390	105.4	0.1632
C6W	195											
C6W	196											
C6W	197											
C6W	198											

C6W	199	13.68	2.96		1.33	124.0	41.89189	93.58490				
C6W	200	13.55	3.18	3.07	1.10	102.0	32.07547	92.55898	36.98368	31.82368	113	0.174967
C6W	201											
C6W	202											
C6W	203											
C6W	204											
C6W	205	13.66	4.19		2.11	180.0	42.95942	85.30805				
C6W	206	13.59	3.28	3.735	1.56	159.0	48.47560	101.9230	45.71751	40.55751	169.5	0.262451
C6W	207											
C6W	208											
C6W	209											
C6W	210											
C6W	211	13.74	2.72		1.14	12.7	4.669117	11.14035				
C6W	212	13.72	3.88	3.3	1.27	12.6	3.247422	9.921259	3.958270	0	12.65	0.019587
C6W	213											
C6W	214											
C6W	215											
C6W	216											
CONI	31	13.90	3.99		1.77	18.4	4.611528	10.39548				
CONI	32	13.46	2.52	3.255	1.14	11.8	4.682539	10.39098	4.647034	0	15.1	0.023380
CONI	33											
CONI	34											
CONI	35											
CONI	36											
CONI	1	13.16	4.48		2.14	17.4	3.883928	8.130841				
CONI	2	13.73	3.19	3.835	1.67	17.6	5.517241	10.53892	4.700584	0	17.5	0.027096
CONI	3											
CONI	4											
CONI	5											
CONI	6											
CONI	7	13.58	3.27		1.35	14.8	4.525993	11.00371				
CONI	8	13.06	3.76	3.515	1.22	15.8	4.202127	12.91905	4.364060	0	15.3	0.023690
CONI	9											
CONI	10											

CONI	11											
CONI	12											
CONI	13	16.60	4.43		1.90	23.8	5.372460	12.5				
CONI	14	13.61	4.56	4.495	1.99	26.6	5.833333	13.39375	5.602896	0.442896	25.2	0.039019
CONI	15											
CONI	16											
CONI	17											
CONI	18											
CONI	19	13.15	1.91		0.97	9.6	5.026178	9.896907				
CONI	20	13.21	4.55	3.23	1.97	17.8	3.912087	9.035532	4.469132	0	13.7	0.021212
CONI	21											
CONI	22											
CONI	23											
CONI	24											
CONI	25	13.75	3.30		1.56	13.2	4	8.461538				
CONI	26	13.83	3.08	3.19	1.42	12.4	4.025974	8.732394	4.012987	0	12.8	0.019819
CONI	27											
CONI	28											
CONI	29											
CONI	30											
CONW	109	13.54	3.16		1.56	17.0	5.379746	10.89743				
CONW	110	13.37	2.43	2.795	0.96	10.6	4.362139	11.04166	4.870943	0	13.8	0.021367
CONW	111											
CONW	112											
CONW	113											
CONW	114											
CONW	115	13.59	4.02		1.80	22.2	5.522388	12.33333				
CONW	116	13.57	2.74	3.38	1.28	13.4	4.890510	10.46875	5.206449	0.046449	17.8	0.027561
CONW	117											
CONW	118											
CONW	119											
CONW	120											

CONV	121	13.63	4.02		1.65	16.2	4.029850	9.848024				
CONV	122	13.65	2.72	3.37	1.16	11.2	4.117647	9.663503	4.073748	0	13.7	0.021212
CONV	123											
CONV	124											
CONV	125											
CONV	126											
CONV	127	13.58	3.49		1.42	20.2	5.787965	14.23537				
CONV	128	13.59	3.11	3.3	1.34	16.6	5.337620	12.39731	5.562793	0.402793	18.4	0.028490
CONV	129											
CONV	130											
CONV	131											
CONV	132											
CONV	133	13.26	3.41		1.61	14.4	4.222873	8.944099				
CONV	134	13.56	3.29	3.35	1.80	15.8	4.802431	8.777777	4.512652	0	15.1	0.023380
CONV	135											
CONV	136											
CONV												
CONV												
CONV		13.80	3.24		1.40	13.0	4.012345	9.305654				
CONV		13.35	2.70	2.97	1.33	12.2	4.518518	9.172932	4.265432	0	12.6	0.019509
CONV												
CONV												
CONV												
CONV												

C8

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		METABOLISM CAGE DATA		URINE CHROMIUM AND CREATININE DATA				
GROUP	ANIMAL NUMBER	URINE IN ml TOTAL	FOR CREAT	URINE Cr ng/ml	URINE CREAT mg/ml	URINE Cr/CREAT	URINE Cr mg/da	MEAN URINE Cr mg/da
C3W	145	11.77	1	16.7	0.52	0.000032	0.000289	
C3W	146	8.30	1	13.8	0.75	0.000018	0.000165	0.000227
C3W	147							
C3W	148							
C3W	149							
C3W	150							
C3W	151	5.02	1	9.8	1.3	0.000007	0.000067	
C3W	152	12.47	1	3.7	0.52	0.000007	0.000064	0.000065
C3W	153							
C3W	154							
C3W	155							
C3W	156							
C3W	157	11.36	1	1.0	0.85	0.000001	0.000010	
C3W	158	17.96	1	6.2	0.8	0.000007	0.000069	0.000040
C3W	159							
C3W	160							
C3W	161							
C3W	162							
C3W	163	11.67	1	1.4	0.8	0.000001	0.000015	
C3W	164	20.24	1	7.8	0.52	0.000015	0.000135	0.000075
C3W	165							
C3W	166							
C3W	167							
C3W	168							
C3W	169	16.80	1	2.3	0.85	0.000002	0.000024	
C3W	170	15.81	1	0.9	0.75	0.000001	0.000010	0.000017
C3W	171							
C3W	172							
C3W	173							
C3W	174							

C3W	175	10.58	1	0.0	0.65	0	0	
C3W	176	13.82	1	0.0	0.8	0	0	0
C3W	177							
C3W	178							
C3W	179							
C3W	180							
C31	67	13.72	17.9	15.4	0.45	0.000034	0.000308	
C31	68	4.00	1	17.9	1.3	0.000013	0.000123	0.000215
C31	69							
C31	70							
C31	71							
C31	72							
C31	37	14.71	1	11.9	0.55	0.000021	0.000194	
C31	38	16.65	1	0.4	0.45	0.000000	0.000008	0.000101
C31	39							
C31	40							
C31	41							
C31	42							
C31	43	14.71	1	6.9	0.7	0.000009	0.000088	
C31	44	16.00	1	5.8	0.65	0.000008	0.000080	0.000084
C31	45							
C31	46							
C31	47							
C31	48							
C31	49	17.04	1	4.3	0.75	0.000005	0.000051	
C31	50	16.95	1	0.9	0.6	0.000001	0.000013	0.000032
C31	51							
C31	52							
C31	53							
C31	54							
C31	55	10.63	1	0.7	1.2	0.000000	0.000005	
C31	56	16.23	1	0.0	0.9	0	0	0.000002

C31	57							
C31	58							
C31	59							
C31	60							
C31	61	4.09	1	0.0	2.4	0	0	
C31	62	21.14	1	0.3	0.75	0.000000	0.000003	0.000001
C31	63							
C31	64							
C31	65							
C31	66							
C61	103	16.59	1	19.5	0.38	0.000051	0.000461	
C61	104	16.95	1	20.6	0.32	0.000064	0.000579	0.000520
C61	105							
C61	106							
C61	107							
C61	108							
C61	73	17.42	1	9.5	0.35	0.000027	0.000244	
C61	74	11.11	1	17.7	0.93	0.000019	0.000171	0.000207
C61	75							
C61	76							
C61	77							
C61	78							
C61	79	15.02	1	13.5	0.75	0.000018	0.000162	
C61	80	25.89	1	16.5	0.4	0.000041	0.000371	0.000266
C61	81							
C61	82							
C61	83							
C61	84							
C61	85	7.93	1	9.9	1.2	0.000008	0.000074	
C61	86	11.02	1	19.0	0.87	0.000021	0.000196	0.000135
C61	87							
C61	88							
C61	89							
C61	90							

C61	91	1.76		13.9	4.2	0.000003	0.000029	
C61	92	4.88		15.8	2.2	0.000007	0.000064	0.000047
C61	93							
C61	94							
C61	95							
C61	96							
C61	97	6.42	1	0.8	1.05	0.000000	0.000006	
C61	98	4.96	1	3.9	1.9	0.000002	0.000018	0.000012
C61	99							
C61	100							
C61	101							
C61	102							
C6W	181	36.02	1	40.1	2.6	0.000015	0.000138	
C6W	182	9.74	1	55.3	0.45	0.000122	0.001106	0.000622
C6W	183							
C6W	184							
C6W	185							
C6W	186							
C6W	187	13.13	1	90.0	0.65	0.000138	0.001246	
C6W	188	22.42	1	90.4	0.35	0.000258	0.002324	0.001785
C6W	189							
C6W	190							
C6W	191							
C6W	192							
C6W	193	17.91	1	117.0	1.4	0.000083	0.000752	
C6W	194	36.68	1	127.0	0.35	0.000362	0.003265	0.002008
C6W	195							
C6W	196							
C6W	197							
C6W	198							

C6W	199	28.88	1	114.0	0.35	0.000325	0.002931	
C6W	200	13.70	1	162.0	0.45	0.00036	0.00324	0.003085
C6W	201							
C6W	202							
C6W	203							
C6W	204							
C6W	205	28.46	1	177.0	0.52	0.000340	0.003063	
C6W	206	14.16	1	117.0	0.8	0.000146	0.001316	0.002189
C6W	207							
C6W	208							
C6W	209							
C6W	210							
C6W	211	26.76	1	21.0	0.67	0.000031	0.000282	
C6W	212	14.09	1	18.8	1.1	0.000017	0.000153	0.000217
C6W	213							
C6W	214							
C6W	215							
C6W	216							
CONI	31	8.44	1	5.3	0.7	0.000007	0.000068	
CONI	32	10.28	1	1.4	0.72	0.000001	0.000017	0.000042
CONI	33							
CONI	34							
CONI	35							
CONI	36							
CONI	1	19.19	1	0.0	0.3	0	0	
CONI	2	6.82	1	0.3	0.7	0.000000	0.000003	0.000001
CONI	3							
CONI	4							
CONI	5							
CONI	6							
CONI	7	10.28	1	0.0	0.8	0	0	
CONI	8	9.26	1	0.0	0.93	0	0	0
CONI	9							
CONI	10							

CONI	11							
CONI	12							
CONI	13	11.32	1	0.0	0.95	0	0	
CONI	14	14.60	1	0.0	0.72	0	0	0
CONI	15							
CONI	16							
CONI	17							
CONI	18							
CONI	19	10.18	1	0.0	0.87	0	0	
CONI	20	8.13	1	0.0	1.3	0	0	0
CONI	21							
CONI	22							
CONI	23							
CONI	24							
CONI	25	9.38	1	0.0	1.4	0	0	
CONI	26	12.68	1	0.1	0.95	0.000000	0.000000	0.000000
CONI	27							
CONI	28							
CONI	29							
CONI	30							
CONW	109	21.58	1	1.0	0.4	0.000002	0.000022	
CONW	110	8.87	1	1.2	0.85	0.000001	0.000012	0.000017
CONW	111							
CONW	112							
CONW	113							
CONW	114							
CONW	115	13.78	1	0.0	0.3	0	0	
CONW	116	7.85	1	0.0	1.05	0	0	0
CONW	117							
CONW	118							
CONW	119							
CONW	120							

CONV	121	16.66	1	0.9	1.05	0.000000	0.000007	
CONV	122	10.56	1	0.0	0.85	0	0	0.000003
CONV	123							
CONV	124							
CONV	125							
CONV	126							
CONV	127	10.31	1	0.0	1.05	0	0	
CONV	128	13.59	1	0.0	0.52	0	0	0
CONV	129							
CONV	130							
CONV	131							
CONV	132							
CONV	133	18.38	1	0.0	0.75	0	0	
CONV	134	4.67	1	4.7	2.1	0.000002	0.000020	0.000010
CONV	135							
CONV	136							
CONV	137							
CONV	138							
CONV	139	30.00	1	0.0	0.27	0	0	
CONV	140	6.62	1	0.0	2	0	0	0
CONV	141							
CONV	142							
CONV	143							
CONV	144							

BLOOD CHROMIUM DATA

ANIMAL NUMBER	GROUP	VOLUMES IN ML: BLOOD	VOLUMES IN ML: BLOOD PLASMA	CHROMIUM CONCENTRATION, ng/ml: PLASMA	WHOLE BLOOD	RBC	MEAN PLASMA	MEAN BLOOD	MEAN RBC	CALC WHOLE BLOOD	PLASMA % TOTAL
145	C3W	5.0	0.6	4.5		1.2				1.596	100
146	C3W	4.0	0.8	3.5		2.3	4.0		1.8	2.54	77.77777
147	C3W	3.6			2.8						
148	C3W	5.0			2.3						
149	C3W	5.2			2.0						
150	C3W	3.4			2.8			2.475			
151	C3W	5.0	1.9	5.1		0.8				2.434	90.26548
152	C3W	4.6	1.9	4.3		1.0	4.7		0.9	2.363043	76.10619
153	C3W	4.8			3.7						
154	C3W	5.2			2.2						
155	C3W	4.0			3.4						
156	C3W	2.0			3.1			3.1075			
157	C3W	5.4	2.3	3.7		1.8				2.609259	12.09509
158	C3W	5.2	2.2	2.7		3.3	3.2		2.6	3.046153	8.826151
159	C3W	5.0			4.9						
160	C3W	5.2			45.8						
161	C3W	4.7			10.8						
162	C3W	1.2			5.8			16.825			
163	C3W	3.0	1.2	2.8		5.1				4.18	27.5
164	C3W	5.4	2.4	3.7		0.7	3.3		2.9	2.033333	36.33928
165	C3W	8.2			4.2						
166	C3W	5.2			4.9						
167	C3W	5.0			6.0						
168	C3W	5.4			7.3			5.6			
169	C3W	5.0	2.3	39.0		2.9				19.506	453.9682
170	C3W	5.0	2.2	4.2		0.0	21.6		1.5	1.826	48.30687
171	C3W	4.0			7.1						
172	C3W	6.8			4.4						
173	C3W	3.6			4.9						
174	C3W	5.4			2.5			4.725			

175	C3W	3.2	1.2	4.8		0.5				2.1125	47.78280
176	C3W	3.4	2.7	4.1		1.9	4.5		1.2	3.647058	40.81447
177	C3W	4.4			12.3						
178	C3W	7.0			3.4						
179	C3W	8.0			3.7						
180	C3W	6.2			2.7			5.525			
67	C31	5.0	0.9	6.3		0.1				1.216	5.636437
68	C31	5.0	1	3.8		0.6	5.1		0.4	1.24	3.399755
69	C31	5.0			46.9						
70	C31	5.4			65.0						
71	C31	5.4			67.0						
72	C31	5.0			67.0			61.475			
37	C31	4.4	1.6	0.0		3.0				1.909090	0
38	C31	5.0	2.2	3.4		3.5	1.7		3.3	3.456	2.888030
39	C31	3.0			196.0						
40	C31	4.2			39.4						
41	C31	5.0			22.9						
42	C31	5.2			0.7			64.75			
43	C31	5.0	2.1	1.8		0.9				1.278	4.230769
44	C31	5.2	2	5.2		1.3	3.5		1.1	2.8	12.22222
45	C31	5.0			0.0						
46	C31	5.4			27.0						
47	C31	5.8			43.6						
48	C31	5.2			23.0			23.4			
49	C31	6.6	2.3	8.6		0.0				2.996969	39.33471
50	C31	5.0	1.9	10.5		51.0	9.6		25.5	35.61	48.02494
51	C31	5.4			0.0						
52	C31	5.4			33.2						
53	C31	5.4			11.9						
54	C31	6.2			3.0			12.025			
55	C31	5.4	2.4	2.2		4.1				3.255555	1.145020
56	C31	10.4	5	2.9		3.4	2.6		3.8	3.159615	1.509344

57	C31	4.6			82.0							
58	C31	5.4			53.0							
59	C31	7.2			235.0			62.56666				
60	C31	4.8			52.7			105.675				
61	C31	8.0	3.6	3.7		3.4					3.535	2.286516
62	C31	8.6	4.4	5.6		0.0	4.7			1.7	2.865116	3.460674
63	C31	7.4			87.0							
64	C31	6.0			97.0							
65	C31	3.4			92.0							
66	C31	5.8			80.0			89				
103	C61	3.2	0.8			0.0					0	MISSING
104	C61	5.0	1.2			16.4	0.0			8.2	12.464	MISSING
105	C61	4.0			56.3							
106	C61	1.8			34.8							
107	C61	4.8			38.0							
108	C61	5.0			40.8			42.475				
73	C61	5.5	2.1	1.4		6.2					4.367272	1.319057
74	C61	5.5	2.3	0.6		6.4	1.0			6.3	3.974545	0.565310
75	C61	5.5			74.0							
76	C61	5.5			54.8							
77	C61	5.0			56.8							
78	C61	5.5			47.9			58.375				
79	C61	5.4	2.1	0.6		7.6					4.877777	0.447457
80	C61	5.6	2.1	74.6		25.0	37.6			16.3	43.6	55.63389
81	C61	4.6			73.0							
82	C61	2.7			84.0							
83	C61	5.4			68.0							
84	C61	5.5			70.0			73.75				
85	C61	5.6	1.7	14.9		25.0					21.93392	11.25300
86	C61	5.8	1.8	10.1		24.9	12.5			25.0	20.30689	7.627875
87	C61	5.6			59.7							
88	C61	5.4			103.0							
89	C61	4.8			38.6							
90	C61	5.6			90.0			72.825				

91	C6I	5.4	2.3	2.5		9.8			6.690740 1.816980
92	C6I	5.4	2.2	1.2		11.0	1.9		10.4 7.007407 0.872150
93	C6I	5.6			73.0				
94	C6I	7.2			114.0				
95	C6I	5.6			71.1				
96	C6I	4.4			44.6			75.675	
97	C6I	6.2	2.8	1.1		2.4			1.812903 1.519146
98	C6I	7.8	3.3	6.0		17.3	3.6		9.9 12.52346 8.300062
99	C6I	7.4			40.8				
100	C6I	7.2			33.3				
101	C6I	6.4			47.0				
102	C6I	7.8			38.2			39.825	
181	C6W	3.6	0.8	MISSING		1.6			1.244444 MISSING
182	C6W	1.8	0.3	3.6		3.1	1.8		2.4 3.183333 22.12290
183	C6W	5.0			6.3				
184	C6W	1.6			9.5				
185	C6W	5.0			8.4				
186	C6W	2.0			11.6			8.95	
187	C6W	3.5	1.2	4.2		4.8			4.584 19.47770
188	C6W	5.5	2.1	9.8		8.3	7.0		6.6 8.872727 45.77494
189	C6W	5.5			17.4				
190	C6W	5.2			7.6				
191	C6W	3.0			6.1				
192	C6W	5.5			16.0			11.775	
193	C6W	1.8	0.7	9.4		7.6			8.3 27.90823
194	C6W	1.4	0.4	9.9		8.6	9.7		8.1 8.971428 29.39271
195	C6W	4.4			14.8				
196	C6W	5.0			27.7				
197	C6W	5.5			12.1				
198	C6W	5.5			19.5			18.525	

199	C6W	5.4	2.3	6.4		10.0				8.466666	7.198364
200	C6W	5.2	2.2	3.3		28.7	4.9		19.4	17.95384	3.711656
201	C6W	5.2			48.0						
202	C6W	4.6			29.8						
203	C6W	5.4			68.9			48.9			
204	C6W	3.2			984.0			282.675			
205	C6W	8.2	2.7	11.2		40.8				31.05365	10.57057
206	C6W	5.4	2	13.4		44.5	12.3		42.7	32.98148	12.64693
207	C6W	3.0			32.3						
208	C6W	5.3			80.7						
209	C6W	5.2			51.8						
210	C6W	6.6			68.3			58.275			
211	C6W	8.4	3.8	6.1		20.5				13.98571	29.69026
212	C6W	7.8	3.3	3.9		19.4	5.0		20.0	12.84230	18.98230
213	C6W	10.4			9.5						
214	C6W	8.2			6.1						
215	C6W	7.2			18.4						
216	C6W	8.4			11.2			11.3			
31	CON1	5.0	1.2	5.0		0.2				1.3472	ERR
32	CON1	5.0	2	1.2		14.5	3.1		7.4	9.18	ERR
33	CON1	3.7			0.0						
34	CON1	5.4			0.0						
35	CON1	3.8			0.0						
36	CON1	5.0			0.0			0			
1	CON1	5.6	2.2	5.7		0.0				2.239285	ERR
2	CON1	4.0	1.5	7.7		5.4	6.7		2.7	6.2625	ERR
3	CON1	5.2			0.0						
4	CON1	4.0			0.0						
5	CON1	3.0			0.0						
6	CON1	1.0			0.0			0			
7	CON1	5.0	2	4.9		4.7				4.78	ERR
8	CON1	5.6	2.3	3.7		18.2	4.3		11.5	12.24464	ERR
9	CON1	4.2			0.0						
10	CON1	5.0			0.0						

11	CONI	3.0			0.0						
12	CONI	5.0			0.0			0			
13	CONI	5.0	2.1	4.1		17.8				12.046	ERR
14	CONI	5.2	2.4	4.0		23.4	4.1		20.6	14.44615	ERR
15	CONI	1.8			0.0						
16	CONI	5.4			0.0						
17	CONI	5.4			0.0						
18	CONI	4.8			0.0			0			
19	CONI	5.4	2.4	1.6		3.0				2.377777	ERR
20	CONI	5.2	1.5	3.6		0.0	2.6		1.5	1.038461	ERR
21	CONI	4.8			0.0						
22	CONI	4.0			0.0						
23	CONI	5.2			0.0						
24	CONI	6.0			0.0			0			
25	CONI	9.6	4.3	3.3		0.0				1.478125	ERR
26	CONI	6.0	3.1	2.4		4.0	2.9		2.0	3.173333	ERR
27	CONI	5.2			0.0						
28	CONI	6.4			0.0						
29	CONI	4.0			0.0						
30	CONI	3.6			0.0			0			
109	CONW	5.0	1	2.1		2.6				2.5	78.30508
110	CONW	3.8	1	3.0		5.5	2.6		4.0	4.812631	111.8644
111	CONW	5.5			1.1						
112	CONW	5.5			2.9						
113	CONW	1.5			1.7						
114	CONW	4.2			0.2			1.475			
115	CONW	2.0	0.6	1.9		5.0				4.07	63.33333
116	CONW	5.5	2	1.9		16.3	1.9		10.7	11.06363	63.33333
117	CONW	5.5			0.0						
118	CONW	5.5			2.2						
119	CONW	5.5			3.0						
120	CONW	5.5			1.4			1.65			

121	CONV	5.2	2.2	2.0		16.5				10.36538	25.88235
122	CONV	5.2	1.6	5.7		19.2	3.9		17.9	15.04615	73.76470
123	CONV	5.2			2.1						
124	CONV	5.4			1.9						
125	CONV	5.2			9.4						
126	CONV	5.4			3.6			4.25			
127	CONV	5.4	2.1	14.7		MISSING				5.716666	234.3478
128	CONV	5.2	1.8	3.3		MISSING	9.0		0.0	1.145769	52.76811
129	CONV	5.5			0.0						
130	CONV	4.4			4.0						
131	CONV	4.8			4.0						
132	CONV	5.4			5.8			3.45			
133	CONV	5.4	2.2	0.3		MISSING				0.122222	2.417582
134	CONV	5.0	2.1	2.2		13.6	1.3		6.8	8.812	17.72893
135	CONV	5.2			9.8						
136	CONV	5.2			5.0						
137	CONV	5.2			6.1						
138	CONV	5.4			6.4			6.825			
139	CONV	8.7	3.9	3.7		6.8				5.410344	81.4
140	CONV	7.8	3.6	4.9		MISSING	4.3		3.4	2.261538	107.8
141	CONV	8.4			0.0						
142	CONV	7.0			2.5						
143	CONV	7.8			3.4						
144	CONV	8.4			4.1			2.5			

GROUP	ANIMAL NUMBER	SACRIFICE NUMBER	TIME	(g) BODY WEIGHT	(ml) BLOOD VOLUME	WEIGHT IN GRAMS LUNG	LIVER TOTAL	LIVER SAMPLE	INTESTINE	KIDNEY	MUSCLE	CARCASS TOTAL	CARCASS SAMPLE	HEAD
C3W	145	1	10.06	234	5.0	1.310	7.654	7.654	4.643	1.840	3.720	155.17	7.268	
C3W	146	1	10.21	233	4.0	1.302	7.231	7.231	4.321	1.753	4.310	155.68	13.356	
C3W	147	1	10.29	239	3.6	1.295	8.160	8.160	4.058	1.708	3.136	142.12	7.626	
C3W	148	1	10.42	232	5.0	1.572	8.720	8.720	3.947	1.704	2.348	133.93	6.001	
C3W	149	1	10.50	231	5.2	1.332	7.648	7.648	5.496	1.667	3.139	131.69	6.309	
C3W	150	1	11.01	231	3.4	1.191	8.448	8.448	4.097	1.694	2.990	130.75	10.547	
C3W	151	2	9.44	258	5.0	1.477	8.553	8.553	6.352	2.008	4.141	160.62	8.959	
C3W	152	2	9.55	237	4.6	1.330	7.430	7.430	5.382	1.725	3.098	159.79	7.622	
C3W	153	2	10.03	234	4.8	1.620	7.966	7.966	4.850	1.726	3.948	135.54	6.457	
C3W	154	2	10.11	245	5.2	1.442	8.101	8.101	5.188	1.745	3.567	142.26	9.762	
C3W	155	2	10.20	223	4.0	1.280	6.731	6.731	6.142	1.547	3.337	135.79	5.659	
C3W	156	2	10.31	224	2.0	1.396	7.289	7.289	4.973	1.540	3.513	133.70	7.506	
C3W	157	3	9.51	265	5.4	1.643	8.422	8.422	5.393	1.780	5.242	177.69	8.814	
C3W	158	3	9.59	292	5.2	1.752	10.377	8.756	5.471	2.189	5.868	192.00	8.412	
C3W	159	3	10.16	269	5.0	1.542	8.580	8.580	6.358	1.932	4.389	158.20	6.136	
C3W	160	3	10.29	271	5.2	1.612	8.600	8.600	4.907	2.029	3.103	158.83	7.748	
C3W	161	3	10.37	280	4.7	1.677	9.101	9.101	7.007	1.987	5.838	161.17	7.876	
C3W	162	3	10.46	263	1.2	1.715	9.162	9.162	4.670	1.960	3.451	148.57	9.276	
C3W	163	4	9.54	272	3.0	1.450	8.170	8.170	8.120	2.230	6.320	187.20	8.660	
C3W	164	4	10.09	273	5.4	1.620	8.240	8.240	5.250	2.130	6.010	190.30	8.310	
C3W	165	4	10.18	320	8.2	1.920	9.520	9.520	6.500	2.270	7.180	185.70	8.760	
C3W	166	4	10.27	291	5.2	1.720	9.610	9.610	5.990	2.150	5.250	171.80	9.410	
C3W	167	4	10.36	302	5.0	1.510	8.770	8.770	4.740	1.940	6.400	183.90	7.990	
C3W	168	4	10.44	290	5.4	1.480	9.570	9.570	7.510	2.260	5.190	174.20	8.340	
C3W	169	5	9.34	351	5.0	2.010	9.970	9.970	6.220	2.590	4.770	246.00	8.850	
C3W	170	5	9.48	360	5.0	2.020	10.330	10.330	5.350	2.560	7.220	250.40	8.230	
C3W	171	5	10.00	341	4.0	2.380	9.500	9.500	6.540	2.500	7.100	211.50	10.350	
C3W	172	5	10.13	341	6.8	1.950	9.420	9.420	7.940	2.340	6.580	205.00	9.870	
C3W	173	5	10.24	295	3.6	2.070	8.820	8.820	5.160	2.010	6.130	183.70	8.480	24.60
C3W	174	5	10.34	235	5.4	1.730	9.820	9.820	5.620	2.600	5.920	206.80	8.860	27.53

C3W	175	6	9.44	359	3.2	1.560	9.540	9.540	8.950	2.380	7.520	249.20	8.570	
C3W	176	6	10.00	360	3.4	1.950	10.600	9.900	9.070	2.460	8.130	253.00	9.360	
C3W	177	6	10.10	374	4.4	1.790	9.870	9.870	9.540	2.610	8.750	228.30	9.080	28.40
C3W	178	6	10.21	371	7.0	1.810	9.360	9.360	7.040	2.570	8.100	229.30	9.190	28.50
C3W	179	6	10.30	410	8.0	3.290	10.700	9.720	6.470	2.920	8.670	251.80	9.620	36.20
C3W	180	6	10.40	321	6.2	1.690	8.650	8.650	5.780	2.300	7.430	199.80	7.140	29.70
C31	67	1	11.17	224	5.0	1.402	7.560	7.560	4.697	1.678	2.905	150.33	8.131	
C31	68	1	11.27	219	5.0	1.404	6.806	6.806	4.219	1.656	2.770	144.31	8.770	
C31	69	1	11.38	267	5.0	1.902	11.244	9.739	10.680	2.034	3.128	153.47	7.360	
C31	70	1	11.49	261	5.4	1.567	10.455	9.680	8.897	1.868	3.808	144.64	10.160	
C31	71	1	11.59	274	5.4	1.480	11.593	10.337	11.217	2.052	3.105	154.26	8.018	
C31	72	1	12.11	244	5.0	1.373	10.094	10.094	10.889	1.818	4.003	136.73	7.830	
C31	37	2	10.40	253	4.4	1.583	8.555	8.555	6.007	1.875	3.227	169.46	8.205	
C31	38	2	10.49	255	5.0	1.934	8.262	8.262	5.622	1.932	4.581	172.59	5.825	
C31	39	2	10.55	223	3.0	1.323	7.069	7.069	4.738	1.665	3.763	129.96	8.361	
C31	40	2	11.06	246	4.2	1.198	7.705	7.705	4.636	1.886	6.273	142.88	9.363	
C31	41	2	11.13	253	5.0	1.482	8.656	8.656	4.255	1.838	5.344	148.18	8.269	
C31	42	2	11.20	251	5.2	1.250	8.269	8.269	3.855	1.835	5.970	147.00	8.487	
C31	43	3	11.01	277	5.0	1.559	8.107	8.107	7.359	2.061	4.805	189.80	6.775	
C31	44	3	11.12	262	5.2	1.574	8.453	8.453	5.325	1.982	3.659	178.16	6.776	
C31	45	3	11.18	265	5.0	1.548	9.010	9.010	4.542	2.020	5.046	156.35	6.652	
C31	46	3	11.27	240	5.4	1.571	6.887	6.887	4.294	1.701	4.149	144.49	8.519	
C31	47	3	11.35	275	5.8	1.782	8.702	8.702	5.143	2.091	4.779	162.03	8.269	
C31	48	3	11.48	257	5.2	1.579	8.199	8.199	5.115	1.785	5.008	148.09	7.540	
C31	49	4	10.55	332	6.6	1.780	9.660	9.660	12.200	2.370	7.650	221.30	7.690	
C31	50	4	11.12	316	5.0	1.510	10.230	9.930	8.280	2.280	6.010	219.70	9.250	
C31	51	4	11.20	295	5.4	1.630	8.530	8.530	4.820	2.170	5.480	184.40	8.120	
C31	52	4	11.27	313	5.4	1.960	9.810	9.810	6.120	2.360	6.090	184.60	8.660	
C31	53	4	11.35	289	5.4	1.770	8.780	8.780	6.310	1.930	5.260	175.30	7.150	
C31	54	4	11.45	287	6.2	1.710	8.850	8.850	5.100	2.040	5.890	172.90	9.020	
C31	55	5	10.44	372	5.4	1.900	9.920	9.920	7.290	2.490	5.440	255.80	8.740	
C31	56	5	10.53	380	10.4	2.040	10.900	10.200	6.520	2.660	5.090	258.90	8.560	

C31	57	5	11.03	373	4.6	1.920	10.500	10.500	4.760	2.570	5.370	234.10	7.670	
C31	58	5	11.11	325	5.4	2.070	9.480	9.480	6.150	2.380	5.830	197.60	7.750	
C31	59	5	11.20	355	7.2	1.720	9.100	9.100	4.800	2.330	5.550	215.30	8.060	29.79
C31	60	5	11.28	327	4.8	1.780	8.600	8.600	5.990	2.290	5.290	205.90	9.020	27.45
C31	61	6	10.50	368	8.0	1.920	9.250	9.250	9.880	2.560	6.170	251.20	7.090	
C31	62	6	11.00	381	8.6	1.930	10.880	10.400	7.070	2.550	6.540	261.30	8.990	
C31	63	6	11.10	391	7.4	1.700	10.000	10.000	8.910	2.380	8.940	235.90	7.940	32.80
C31	64	6	11.19	398	6.0	1.920	10.300	10.300	5.710	2.460	9.440	237.20	9.190	30.40
C31	65	6	11.28	405	3.4	1.880	10.900	10.100	6.540	2.930	10.100	258.80	9.380	34.80
C31	66	6	11.39	363	5.8	1.530	8.440	8.440	6.720	2.310	9.560	227.60	9.820	27.30
C61	103	1	11.20	228	3.2	1.380	7.540	7.540	5.340	1.690	3.680	152.45	8.110	
C61	104	1	11.30	237	5.0	1.350	7.050	7.050	5.320	1.750	4.330	156.96	8.580	
C61	105	1	11.41	256	4.0	1.330	10.100	10.100	12.380	1.830	3.770	140.14	11.900	
C61	106	1	11.53	254	1.8	1.390	10.230	9.940	10.060	2.060	3.660	143.23	10.650	
C61	107	1	12.07	261	4.8	1.440	10.830	9.720	14.370	2.110	4.380	144.90	9.160	
C61	108	1	12.19	251	5.0	1.360	11.020	9.140	9.330	1.950	3.990	144.75	9.510	
C61	73	2	10.44	247	5.5	1.260	7.900	7.900	4.580	1.880	4.450	164.20	7.700	
C61	74	2	10.49	250	5.5	1.360	7.750	7.750	5.240	1.770	3.500	167.40	8.330	
C61	75	2	10.58	248	5.5	1.390	8.250	8.250	6.380	1.870	3.530	146.00	8.020	
C61	76	2	11.04	238	5.5	1.640	7.870	7.870	6.370	1.840	4.200	136.00	7.740	
C61	77	2	11.10	238	5.0	1.070	7.190	7.190	4.650	1.630	3.720	142.10	8.930	
C61	78	2	11.17	236	5.5	1.330	7.510	7.510	6.100	1.680	3.770	138.80	8.940	
C61	79	3	11.05	278	5.4	1.350	9.430	9.430	6.180	2.040	5.670	187.40	8.940	
C61	80	3	11.15	263	5.6	1.360	8.770	8.770	7.140	1.920	5.290	177.60	9.140	
C61	81	3	11.23	253	4.6	1.480	8.370	8.370	4.480	1.760	4.410	148.40	7.530	
C61	82	3	11.30	263	2.7	1.590	9.740	9.740	4.310	2.120	5.820	155.20	9.270	
C61	83	3	11.44	270	5.4	1.440	8.730	8.730	5.720	2.360	5.220	154.50	8.820	
C61	84	3	11.52	271	5.5	1.430	7.870	7.870	6.760	1.840	5.390	157.40	7.530	
C61	85	4	11.05	283	5.6	1.730	8.560	8.560	9.050	2.290	5.510	194.43	7.540	
C61	86	4	11.16	302	5.8	2.040	9.670	9.670	6.380	2.330	6.910	205.54	7.300	
C61	87	4	11.23	272	5.6	1.440	7.940	7.940	7.250	1.860	6.610	156.26	7.900	
C61	88	4	11.32	315	5.4	1.940	10.540	10.540	6.360	2.510	6.550	192.57	8.370	
C61	89	4	11.40	275	4.8	1.450	7.990	7.990	5.300	2.080	7.080	164.21	8.930	
C61	90	4	11.48	288	5.6	1.490	8.430	8.430	4.720	2.280	5.700	170.21	7.100	

C61	91	5	10.49	342	5.4	1.930	9.710	9.710	5.840	2.330	8.550	235.59	9.480	
C61	92	5	10.58	352	5.4	1.800	9.780	9.780	5.620	2.590	8.750	246.21	9.480	
C61	93	5	11.07	291	5.6	1.650	8.670	8.670	6.440	2.150	7.620	175.68	8.450	23.80
C61	94	5	11.16	371	7.2	1.730	10.130	9.110	5.860	2.690	9.130	230.96	9.330	28.90
C61	95	5	11.25	330	5.6	1.740	8.740	8.740	5.340	2.430	8.400	204.53	8.560	28.10
C61	96	5	11.33	352	4.4	1.910	11.520	9.650	7.100	2.550	7.050	219.08	9.070	26.30
C61	97	6	10.55	393	6.2	1.660	11.580	10.330	7.110	3.030	9.480	270.58	9.410	
C61	98	6	11.06	327	7.8	1.620	10.120	10.120	7.070	2.430	7.620	220.10	8.110	
C61	99	6	11.15	350	7.4	1.420	9.600	9.600	6.920	2.520	8.160	213.34	8.370	28.29
C61	100	6	11.24	386	7.2	1.080	10.840	9.720	6.210	2.900	9.000	239.01	8.970	32.84
C61	101	6	11.32	355	6.4	2.050	9.450	9.450	5.660	2.740	8.160	220.39	9.780	28.52
C61	102	6	11.44	387	7.8	1.850	11.850	10.480	6.010	3.120	9.870	238.00	9.250	29.77
C6W	181	1	10.10	228	3.6	1.210	7.020	7.020	5.550	1.690	2.650	149.41	11.840	
C6W	182	1	10.24	239	1.8	1.320	7.920	7.920	6.960	1.980	3.510	159.45	9.450	
C6W	183	1	10.37	236	5.0	1.440	7.590	7.590	5.690	1.790	3.430	131.59	10.270	
C6W	184	1	10.45	233	1.6	1.280	7.850	7.850	5.820	1.860	3.810	132.14	10.000	
C6W	185	1	10.55	247	5.0	1.260	7.810	7.810	6.420	1.700	3.840	142.28	8.570	
C6W	186	1	11.05	227	2.0	1.350	7.280	7.280	4.420	1.560	3.530	134.78	11.000	
C6W	187	2	9.50	257	3.5	1.520	10.550	9.650	6.140	2.080	2.350	170.70	8.460	
C6W	188	2	10.00	232	5.5	1.230	7.320	7.320	4.920	1.720	3.750	150.60	8.330	
C6W	189	2	10.09	241	5.5	1.320	8.630	8.630	6.440	1.970	4.350	142.20	8.260	
C6W	190	2	10.15	265	5.2	1.480	8.870	8.870	5.680	2.080	4.080	160.30	8.760	
C6W	191	2	10.23	252	3.0	1.280	9.240	9.240	5.510	2.130	4.650	151.90	8.280	
C6W	192	2	10.35	252	5.5	2.330	7.620	7.620	4.170	1.980	3.940	149.10	9.760	
C6W	193	3	9.55	276	1.8	1.390	10.170	9.510	7.440	2.110	5.390	184.40	8.580	
C6W	194	3	10.07	261	1.4	1.840	10.030	9.460	5.290	2.220	4.750	172.90	9.880	
C6W	195	3	10.20	283	4.4	1.280	9.190	9.190	4.680	2.120	3.830	165.00	7.430	
C6W	196	3	10.33	250	5.0	1.240	7.790	7.790	4.720	1.840	4.710	144.40	7.850	
C6W	197	3	10.41	259	5.5	1.330	8.810	8.810	5.960	2.050	4.460	150.70	7.600	
C6W	198	3	10.50	262	5.5	1.820	8.560	8.560	6.170	2.040	4.260	153.40	8.770	

C6W	199	4	10.01	308	5.4	1.790	10.950	9.030	6.830	2.500	5.600	211.47	7.870	
C6W	200	4	10.13	294	5.2	2.330	9.160	9.160	6.880	2.250	6.260	203.82	8.430	
C6W	201	4	10.22	313	5.2	1.930	9.260	9.290	6.600	2.460	6.090	192.21	8.100	
C6W	202	4	10.32	280	4.6	1.320	8.160	8.160	7.370	2.000	6.650	166.75	8.250	
C6W	203	4	10.41	274	5.4	1.800	7.730	7.730	5.220	1.800	6.500	169.70	8.310	
C6W	204	4	10.49	307	3.2	1.650	9.370	9.370	4.870	2.120	6.200	183.83	7.980	
C6W	205	5	9.44	369	8.2	1.650	9.770	9.770	10.600	2.340	9.000	256.59	8.940	
C6W	206	5	9.55	314	5.4	1.510	9.480	9.480	4.940	2.460	7.960	216.04	7.270	
C6W	207	5	10.05	342	3.0	1.430	10.090	9.630	5.860	2.800	8.510	215.95	9.050	26.40
C6W	208	5	10.18	321	5.3	1.490	8.520	8.520	6.170	2.440	7.880	202.56	8.670	26.60
C6W	209	5	10.29	241	5.2	2.190	9.560	9.560	7.290	2.280	7.140	209.39	9.140	28.10
C6W	210	5	10.39	347	6.6	1.620	10.020	9.600	5.650	2.430	8.890	214.63	8.280	29.00
C6W	211	6	9.48	391	8.4	1.970	11.580	9.960	9.870	2.960	9.050	270.30	9.310	
C6W	212	6	10.03	381	7.8	1.860	10.920	9.860	5.040	2.540	8.520	261.20	8.050	
C6W	213	6	10.15	386	10.4	1.700	10.140	10.140	5.770	2.540	9.540	242.70	9.570	29.38
C6W	214	6	10.27	373	8.2	2.780	9.210	9.210	7.890	2.400	9.900	225.50	10.560	32.72
C6W	215	6	10.36	366	7.2	1.900	10.520	10.520	6.100	2.760	8.590	221.50	7.920	30.80
C6W	216	6	10.45	379	8.4	2.140	10.370	10.370	6.570	2.770	10.280	231.20	9.400	30.80
CONI	31	1	8.45	226.5	5.0	1.270	8.235	8.235	5.831	1.718	1.820	152.43	22.000	
CONI	32	1	9.00	250	5.0	1.383	9.306	9.306	6.010	1.840	1.954	168.59	9.562	
CONI	33	1	9.17	253	3.7	1.356	10.884	9.461	10.523	1.728	2.591	146.75	11.740	
CONI	34	1	9.30	251	5.4	1.230	11.227	10.079	9.685	1.844	3.204	149.30	12.215	
CONI	35	1	9.38	278	3.8	1.373	11.598	9.086	12.864	1.786	3.725	160.89	10.356	
CONI	36	1	9.54	247	5.0	1.340	9.713	9.713	7.821	1.751	3.505	141.60	10.044	
CONI	1	2	8.48	256	5.6	1.488	8.332	8.332	5.061	1.971	2.937	166.98	6.800	
CONI	2	2	8.55	234	4.0	1.276	7.496	7.496	4.635	1.743	2.800	155.60	7.969	
CONI	3	2	9.04	238	5.2	1.412	7.689	7.689	3.954	1.655	3.205	136.91	8.446	
CONI	4	2	9.11	233	4.0	1.854	8.322	8.322	3.657	1.745	2.829	135.61	8.045	
CONI	5	2	9.20	255	3.0	1.265	8.537	8.537	4.909	1.753	3.889	150.92	7.304	
CONI	6	2	9.31	249	1.0	1.403	8.681	8.681	4.754	1.973	3.798	148.25	7.808	
CONI	7	3	8.52	258	5.0	1.706	7.646	7.646	4.987	1.710	3.650	174.88	5.902	
CONI	8	3	9.03	283	5.6	1.806	8.006	8.006	6.157	2.038	4.234	193.90	5.697	
CONI	9	3	9.13	265	4.2	2.034	7.940	7.940	6.510	1.807	4.531	159.78	7.128	
CONI	10	3	9.24	268	5.0	1.387	8.204	8.204	5.618	1.786	5.107	157.21	9.215	

CONI	11	3	9.35	282	3.0	1.684	9.096	9.096	6.245	2.111	4.662	172.03	7.710	
CONI	12	3	9.44	250	5.0	1.916	8.074	8.074	4.451	1.838	4.762	142.10	7.813	
CONI	13	4	8.45	326	5.0	1.760	10.090	10.090	6.550	2.230	4.830	223.30	8.410	
CONI	14	4	9.00	329	5.2	1.670	10.100	10.100	9.440	2.400	6.340	220.60	8.040	
CONI	15	4	9.15	350	1.8	1.980	11.480	9.840	6.780	2.640	6.410	217.90	8.300	
CONI	16	4	9.27	286	5.4	1.520	7.910	7.910	6.440	2.140	6.160	164.70	7.190	
CONI	17	4	9.36	283	5.4	1.470	8.240	8.240	5.340	1.930	6.550	171.10	7.520	
CONI	18	4	9.45	291	4.8	1.530	8.900	8.900	4.870	2.170	6.650	177.50	9.070	
CONI	19	5	8.43	298	5.4	2.020	8.120	8.120	6.330	2.060	3.070	204.10	8.740	
CONI	20	5	8.50	358	5.2	1.870	13.140	9.880	5.670	2.840	6.050	239.70	7.000	
CONI	21	5	8.56	360	4.8	2.090	9.370	9.370	6.320	2.430	7.020	218.20	8.980	
CONI	22	5	9.07	321	4.0	1.890	9.000	9.000	6.090	2.200	5.910	190.40	7.260	
CONI	23	5	9.14	328	5.2	1.690	9.190	9.190	7.200	2.270	5.190	202.70	8.840	29.33
CONI	24	5	9.24	363	6.0	1.790	10.100	10.100	6.850	2.730	5.810	224.20	8.580	30.32
CONI	25	6	8.47	385	9.6	1.760	10.100	10.100	6.770	2.540	6.450	259.90	9.770	
CONI	26	6	8.55	380	6.0	1.830	10.100	10.100	7.280	2.580	6.520	260.20	9.430	
CONI	27	6	9.04	357	5.2	1.970	9.510	9.510	5.580	2.550	7.050	219.40	8.040	32.40
CONI	28	6	9.13	382	6.4	1.640	9.460	9.460	6.650	2.380	7.280	229.80	8.820	28.70
CONI	29	6	9.21	379	4.0	2.180	10.300	10.300	5.620	2.710	7.130	235.90	7.890	31.00
CONI	30	6	9.31	373	3.6	1.850	10.700	10.200	7.690	2.680	7.130	230.90	7.570	28.60
CONW	109	1	8.45	264	5.0	1.470	8.910	8.910	4.520	1.970	4.070	173.07	10.990	
CONW	110	1	9.12	247	3.8	1.410	10.090	9.850	7.710	2.060	3.160	161.05	12.520	
CONW	111	1	9.26	236	5.5	1.050	7.490	7.490	5.770	1.700	4.080	134.55	10.050	
CONW	112	1	9.35	233	5.5	1.470	8.090	8.090	4.430	1.770	3.470	130.35	9.690	
CONW	113	1	9.42	241	1.5	1.240	7.620	7.620	4.950	1.800	4.040	139.89	7.230	
CONW	114	1	9.59	237	4.2	1.290	7.740	7.740	7.160	1.890	3.460	130.68	6.930	
CONW	115	2	8.57	248	2.0	1.290	9.930	9.930	6.200	2.010	3.690	164.35	8.750	
CONW	116	2	9.08	247	5.5	1.990	8.380	8.380	5.390	1.920	4.070	161.38	9.020	
CONW	117	2	9.15	236	5.5	1.340	7.820	7.820	4.760	1.790	3.150	137.79	9.260	
CONW	118	2	9.28	257	5.5	1.320	8.530	8.530	6.310	1.870	3.370	146.60	7.820	
CONW	119	2	9.37	237	5.5	1.470	8.080	8.080	5.210	1.720	3.010	136.50	8.040	
CONW	120	2	9.44	250	5.5	1.560	8.640	8.640	6.160	1.900	3.860	148.30	10.470	

CONW	121	3	8.56	289	5.2	1.400	9.170	9.170	9.130	2.340	5.130	193.00	7.660	
CONW	122	3	9.10	266	5.2	1.420	8.260	8.260	4.830	1.980	4.060	180.60	8.130	
CONW	123	3	9.20	241	5.2	1.220	7.550	7.550	4.300	1.690	4.110	141.30	7.000	
CONW	124	3	9.30	257	5.4	1.170	7.800	7.800	6.200	1.820	4.560	147.80	8.210	
CONW	125	3	9.40	281	5.2	1.470	8.690	8.690	6.250	2.160	4.000	171.20	9.260	
CONW	126	3	9.48	267	5.4	2.040	8.050	8.050	5.730	1.800	5.870	151.80	7.720	
CONW	127	4	8.43	323	5.4	1.590	9.530	9.530	7.870	2.260	5.280	219.98	8.030	
CONW	128	4	8.54	306	5.2	1.320	9.410	9.410	6.510	2.510	6.980	211.11	7.510	
CONW	129	4	9.08	306	5.5	1.740	8.670	8.670	4.690	2.170	6.480	189.35	8.180	
CONW	130	4	9.20	300	4.4	1.780	9.190	9.190	6.270	2.190	5.400	181.33	7.560	
CONW	131	4	9.30	330	4.8	1.800	10.170	7.760	7.280	2.510	6.340	205.47	9.190	
CONW	132	4	9.49	291	5.4	1.520	8.210	8.210	8.160	2.130	7.990	160.88	7.630	
CONW	133	5	8.44	359	5.4	1.790	10.160	9.710	8.600	2.780	7.970	245.14	7.910	
CONW	134	5	8.51	335	5.0	1.760	9.600	9.600	6.460	2.380	7.960	240.57	7.060	
CONW	135	5	9.01	335	5.2	1.730	9.720	9.720	6.170	2.400	7.880	198.28	8.230	33.90
CONW	136	5	9.10	343	5.2	2.000	10.050	9.580	6.470	2.540	9.380	212.05	7.770	33.00
CONW	137	5	9.20	337	5.2	1.870	8.220	8.220	7.980	2.390	6.840	220.22	8.140	26.70
CONW	138	5	9.30	335	5.4	1.720	9.700	9.700	7.890	2.410	8.380	200.93	7.850	27.76
CONW	139	6	8.48	371	8.7	1.660	10.210	10.210	7.200	2.940	7.470	260.60	6.200	
CONW	140	6	9.00	352	7.8	1.540	9.420	9.420	5.660	2.320	8.500	247.70	9.100	
CONW	141	6	9.09	352	8.4	1.570	8.990	8.990	5.120	2.540	8.330	215.50	10.460	28.60
CONW	142	6	9.17	365	7.0	1.680	10.130	10.130	6.930	2.790	7.990	223.50	8.890	
CONW	143	6	9.28	363	7.8	1.760	9.390	9.390	8.670	2.840	9.100	219.75	11.300	28.65
CONW	144	6	9.38	382	8.4	1.920	10.910	10.910	6.300	3.020	8.230	236.60	10.030	31.80

ug Chromium per sample

GROUP	ANIMAL NUMBER	LUNG	LIVER	INTEST	KIDNEY	MUSCLE	CARCASS
C3W	145	0.2	0.3	8.3	0.2	0.2	1.7
C3W	146	0.2	0.3	5.6	0.2	0.2	2.5
C3W	147	0.2	0.3	106.0	0.2	0.2	2.5
C3W	148	0.2	0.3	89.0	0.2	0.2	1.4
C3W	149	0.2	0.4	223.0	0.2	0.2	1.3
C3W	150	0.2	0.4	71.0	0.2	0.2	3.9
		0.2	0.333333	83.81666	0.2	0.2	2.216666
		ERR	0.047140	72.88786	ERR	ERR	0.891471
C3W	151	0.9	0.4	40.0	0.2	0.2	1.3
C3W	152	0.2	0.4	27.5	0.2	0.2	1.3
C3W	153	0.2	0.3	125.0	0.2	0.2	1.6
C3W	154	0.4	0.2	89.0	0.2	0.2	1.4
C3W	155	0.2	0.2	81.0	0.8	0.2	1.4
C3W	156	0.2	0.2	179.0	0.2	0.2	1.3
		0.35	0.283333	90.25	0.3	0.2	1.383333
		0.256580	0.089752	51.04552	0.223606	ERR	0.106718
C3W	157	0.2	0.3	53.0	0.2	0.2	2.0
C3W	158	0.2	0.3	38.0	0.2	0.2	1.5
C3W	159	0.2	0.3	182.0	0.2	0.2	8.0
C3W	160	0.2	0.3	129.0	0.2	0.2	3.2
C3W	161	0.2	0.3	85.0	0.2	0.2	1.7
C3W	162	0.7	0.3	186.0	0.2	0.2	6.4
		0.283333	0.3	112.1666	0.2	0.2	3.8
		0.186338	ERR	58.23920	ERR	ERR	2.506657
C3W	163	0.2	0.2	66.0	0.2	0.2	1.3
C3W	164	0.2	0.2	62.0	0.2	0.3	1.6
C3W	165	0.2	0.2	245.0	0.2	0.3	3.1
C3W	166	0.2	0.2	270.0	0.2	0.3	2.6
C3W	167	0.2	0.2	105.0	0.2	0.2	2.1
C3W	168	0.2	0.2	270.0	0.2	0.2	2.2
		0.2	0.2	169.6666	0.2	0.25	2.15
		ERR	ERR	93.38926	ERR	0.05	0.596517
C3W	169	0.2	0.2	38.0	0.2	0.2	1.8
C3W	170	0.2	0.2	32.0	0.2	0.2	1.6
C3W	171	0.2	0.2	50.0	0.2	0.2	2.4
C3W	172	0.2	0.2	86.0	0.2	0.2	2.2

C3W	173	0.2	0.2	38.5	0.2	0.2	1.6
C3W	174	0.2	0.2	27.5	0.2	0.2	2.3
		0.2	0.2	45.33333	0.2	0.2	1.983333
		ERR	ERR	19.45864	ERR	ERR	0.328718
C3W	175	0.2	0.2	6.7	0.2	0.2	1.8
C3W	176	0.2	0.3	8.1	0.2	0.3	2.2
C3W	177	0.2	0.3	7.0	0.2	0.2	1.3
C3W	178	0.2	0.2	6.7	0.2	0.2	1.9
C3W	179	0.2	0.3	4.8	0.2	0.2	1.7
C3W	180	1.4	0.3	5.2	0.2	0.2	1.7
		0.4	0.266666	6.416666	0.2	0.216666	1.766666
		0.447213	0.047140	1.112679	ERR	0.037267	0.268741
C3I	67	3.4	0.2	71.0	0.2	0.2	1.3
C3I	68	3.2	0.2	3.6	0.2	0.2	2.4
C3I	69	4.6	0.2	12.8	0.2	0.2	2.6
C3I	70	3.2	0.2	9.8	0.2	0.2	2.8
C3I	71	3.0	0.2	23.0	0.2	0.2	1.6
C3I	72	3.2	0.2	12.2	0.2	0.2	1.0
		3.433333	0.2	22.06666	0.2	0.2	1.95
		0.534373	ERR	22.62024	ERR	ERR	0.682519
C3I	37	9.0	0.2	100.0	0.2	0.2	2.1
C3I	38	8.0	0.2	10.8	0.2	0.2	1.0
C3I	39	8.4	0.2	12.6	0.2	0.2	1.0
C3I	40	7.0	0.2	7.0	0.2	0.2	1.2
C3I	41	9.8	0.2	5.6	0.2	0.2	1.4
C3I	42	8.4	0.2	4.2	0.2	0.3	1.4
		8.433333	0.2	23.36666	0.2	0.216666	1.35
		0.859586	ERR	34.39329	ERR	0.037267	0.373050
C3I	43	16.8	0.2	112.0	0.2	0.2	1.7
C3I	44	17.6	0.2	8.8	0.2	0.2	1.6
C3I	45	17.0	0.2	4.2	0.2	0.2	1.0
C3I	46	15.6	0.2	7.0	0.2	0.2	1.5
C3I	47	18.2	0.2	10.4	0.2	0.2	1.7
C3I	48	17.4	0.2	11.4	0.2	0.2	7.7
		17.1	0.2	25.63333	0.2	0.2	2.533333
		0.806225	ERR	38.69494	ERR	ERR	2.322833
C3I	49	39.2	0.2	148.0	0.2	0.2	1.8
C3I	50	27.9	0.2	32.0	0.2	0.2	1.7
C3I	51	33.9	0.2	14.4	5.0	0.2	1.3
C3I	52	38.7	0.2	15.0	0.2	0.2	1.8

C3I	53	38.2	0.2	17.2	0.2	0.2	1.4
C3I	54	34.2	0.2	10.0	0.2	0.2	1.4
		35.35	0.2	39.43333	1	0.2	1.566666
		3.939014	ERR	49.03446	1.788854	ERR	0.205480
C3I	55	65.0	0.2	78.0	0.2	0.3	5.6
C3I	56	65.0	0.2	34.8	0.2	0.2	1.8
C3I	57	75.5	0.2	9.4	0.2	0.2	0.8
C3I	58	54.5	0.2	18.0	0.2	0.2	1.3
C3I	59	62.0	0.2	14.4	0.2	0.2	1.4
C3I	60	60.0	0.2	29.2	0.2	0.3	1.2
		63.66666	0.2	30.63333	0.2	0.233333	2.016666
		6.374863	ERR	22.86552	ERR	0.047140	1.629331
C3I	61	44.5	0.2	14.4	0.2	0.2	1.0
C3I	62	39.5	0.2	5.2	0.2	0.3	1.2
C3I	63	46.0	0.2	4.2	0.2	0.3	1.0
C3I	64	37.0	0.2	6.0	0.2	0.4	1.6
C3I	65	50.0	0.2	2.8	0.2	0.3	2.0
C3I	66	40.5	0.2	6.2	0.2	0.3	1.8
		42.91666	0.2	6.466666	0.2	0.3	1.433333
		4.372419	ERR	3.728568	ERR	0.057735	0.390156
C6I	103	1.9	0.2	4.9	0.2	0.2	1.5
C6I	104	1.7	0.2	8.7	0.2	0.2	0.9
C6I	105	1.8	0.2	16.5	0.2	0.2	1.6
C6I	106	2.0	0.2	13.9	0.2	0.2	1.2
C6I	107	2.2	0.2	11.7	0.2	0.2	1.3
C6I	108	2.1	0.2	9.7	0.2	0.2	1.2
		1.95	0.2	10.9	0.2	0.2	1.283333
		0.170782	ERR	3.725587	ERR	ERR	0.226691
C6I	73	4.1	0.4	6.0	0.2	0.2	1.6
C6I	74	5.0	0.5	7.2	0.4	0.2	1.5
C6I	75	5.4	0.5	8.0	0.5	0.2	1.6
C6I	76	3.6	0.4	7.0	0.4	0.2	1.4
C6I	77	4.2	0.5	5.1	0.4	0.2	1.5
C6I	78	8.3	0.5	3.7	0.4	0.2	1.3
		5.1	0.466666	6.166666	0.383333	0.2	1.483333
		1.549193	0.047140	1.436043	0.089752	ERR	0.106718
C6I	79	6.7	0.7	7.3	0.4	0.2	1.9
C6I	80	8.1	0.5	14.7	0.4	0.2	1.5
C6I	81	7.2	0.7	3.2	0.6	0.2	1.0
C6I	82	8.2	0.5	4.5	0.5	0.2	1.5

C6I	83	7.2	0.5	6.9	0.4	0.2	1.0
C6I	84	7.8	0.4	13.5	0.5	0.2	0.9
		7.533333	0.55	8.35	0.466666	0.2	1.3
		0.540575	0.111803	4.308808	0.074535	ERR	0.360555
C6I	85	13.6	0.5	16.5	0.8	0.3	1.3
C6I	86	12.4	0.7	16.7	0.4	0.2	1.0
C6I	87	11.8	0.5	17.5	0.6	0.3	1.3
C6I	88	15.0	0.6	15.7	0.7	0.4	1.4
C6I	89	13.0	0.7	13.1	0.8	0.3	1.2
C6I	90	14.2	0.5	11.1	0.8	0.3	1.4
		13.33333	0.583333	15.1	0.683333	0.3	1.266666
		1.074967	0.089752	2.259793	0.146249	0.057735	0.137436
C6I	91	25.5	0.7	22.2	4.2	0.6	2.3
C6I	92	26.0	0.7	22.2	0.6	0.4	2.9
C6I	93	20.8	1.0	17.4	1.0	0.4	2.0
C6I	94	22.0	0.9	16.6	0.8	0.4	1.3
C6I	95	24.5	0.9	17.0	0.9	0.6	6.0
C6I	96	26.9	0.7	21.2	0.8	0.3	1.8
		24.28333	0.816666	19.43333	1.383333	0.45	2.716666
		2.185876	0.121335	2.466891	1.265459	0.111803	1.546411
C6I	97	12.0	0.4	7.5	0.3	0.2	1.3
C6I	98	15.4	0.4	6.1	0.3	0.3	1.6
C6I	99	12.6	0.4	7.1	0.3	0.2	1.5
C6I	100	10.8	0.3	5.3	0.3	0.2	1.0
C6I	101	11.4	0.4	2.3	0.5	0.2	1.6
C6I	102	15.8	0.4	4.2	0.6	0.3	1.1
		13	0.383333	5.416666	0.383333	0.233333	1.35
		1.921804	0.037267	1.772396	0.121335	0.047140	0.236290
C6W	181	0.2	1.3	46.0	0.3	0.2	2.8
C6W	182	0.2	1.1	42.0	0.3	0.2	1.1
C6W	183	0.2	1.6	86.0	0.5	0.2	3.0
C6W	184	0.2	1.9	89.0	0.5	0.2	2.4
C6W	185	0.2	1.9	180.0	0.5	0.2	3.0
C6W	186	0.2	1.7	90.0	0.5	0.5	5.9
		0.2	1.583333	88.83333	0.433333	0.25	3.033333
		ERR	0.296741	45.36671	0.094280	0.111803	1.438363
C6W	187	0.2	2.8	53.0	0.8	0.2	2.1
C6W	188	0.2	2.6	15.3	0.8	0.2	1.6
C6W	189	0.2	3.9	279.0	2.2	0.2	2.9
C6W	190	0.2	2.2	53.0	0.9	0.2	1.8

C6W	191	0.2	3.6	130.0	1.0	0.2	2.1
C6W	192	0.4	3.8	202.0	1.3	0.3	5.1
		0.233333	3.15	122.05	1.166666	0.216666	2.6
		0.074535	0.647430	93.11272	0.492160	0.037267	1.188836
C6W	193	0.2	5.0	106.5	1.6	0.2	2.3
C6W	194	0.2	6.1	46.0	2.2	0.2	2.8
C6W	195	0.2	4.5	43.5	1.7	0.2	2.4
C6W	196	0.2	6.3	74.5	6.2	0.2	1.6
C6W	197	0.2	3.8	126.0	5.6	0.2	3.1
C6W	198	0.2	5.2	107.0	2.0	0.2	4.2
		0.2	5.15	83.91666	3.216666	0.2	2.733333
		ERR	0.865544	31.55341	1.915216	ERR	0.803464
C6W	199	0.2	5.7	43.5	2.6	0.3	1.5
C6W	200	2.9	11.4	76.0	3.1	0.4	3.1
C6W	201	0.5	11.7	291.0	3.8	0.4	2.3
C6W	202	0.3	8.4	218.0	5.0	0.6	2.8
C6W	203	2.7	14.2	301.0	4.3	0.7	4.4
C6W	204	0.4	9.9	124.0	3.0	0.5	6.4
		1.166666	10.21666	175.5833	3.633333	0.483333	3.416666
		1.159980	2.685402	100.7250	0.825967	0.134370	1.595218
C6W	205	0.5	12.9	66.0	4.4	1.0	4.2
C6W	206	0.7	17.4	57.0	4.4	0.7	2.4
C6W	207	0.6	11.8	27.0	4.4	0.9	3.5
C6W	208	0.7	14.9	28.0	5.1	0.9	3.2
C6W	209	0.7	16.0	51.0	4.8	0.7	2.6
C6W	210	0.7	11.8	38.0	4.8	0.9	3.2
		0.65	14.13333	44.5	4.65	0.85	3.183333
		0.076376	2.127335	14.61449	0.269258	0.111803	0.589962
C6W	211	0.5	4.7	10.1	2.1	0.8	4.0
C6W	212	0.4	4.9	4.3	1.5	0.5	3.0
C6W	213	0.4	3.9	4.5	1.2	0.5	3.6
C6W	214	0.5	5.3	2.6	1.4	0.7	3.5
C6W	215	0.4	6.0	5.1	2.2	0.7	2.3
C6W	216	0.5	5.8	7.7	1.8	0.7	2.6
		0.45	5.1	5.716666	1.7	0.65	3.166666
		0.05	0.704745	2.474144	0.365148	0.111803	0.590668
CONI	31	0.2	0.4	4.0	0.2	0.2	3.6
CONI	32	0.2	0.5	5.6	0.2	0.2	3.4
CONI	33	0.2	0.3	13.4	0.2	0.2	3.4
CONI	34	0.2	0.3	13.6	0.2	0.2	2.9

CONI	35	0.2	0.3	17.0	0.2	0.2	2.1
CONI	36	0.2	0.2	9.2	0.2	0.2	1.8
		0.2	0.333333	10.46666	0.2	0.2	2.866666
		ERR	0.094280	4.622649	ERR	ERR	0.687184
CONI	1	0.2	0.4	3.6	0.2	0.2	0.8
CONI	2	0.2	0.3	2.6	0.2	0.2	1.1
CONI	3	0.2	0.3	1.7	0.2	0.2	0.8
CONI	4	0.2	0.4	1.8	0.2	0.2	1.0
CONI	5	0.2	0.3	3.2	0.2	0.2	1.2
CONI	6	0.2	0.3	4.7	0.2	0.2	0.8
		0.2	0.333333	2.933333	0.2	0.2	0.95
		ERR	0.047140	1.045094	ERR	ERR	0.160727
CONI	7	0.2	0.2	2.2	0.2	0.2	2.4
CONI	8	0.2	0.2	6.4	0.2	0.2	1.9
CONI	9	0.2	0.2	7.4	0.2	0.2	5.0
CONI	10	0.2	0.2	4.6	0.2	2.0	2.2
CONI	11	0.2	0.2	7.4	0.2	0.2	1.4
CONI	12	0.2	0.2	1.5	0.2	0.2	1.6
		0.2	0.2	4.916666	0.2	0.5	2.416666
		ERR	ERR	2.369540	ERR	0.670820	1.203351
CONI	13	0.2	0.2	6.2	0.5	0.2	15.5
CONI	14	0.2	0.3	13.2	0.2	0.2	1.2
CONI	15	0.2	0.3	5.8	0.2	0.2	1.2
CONI	16	0.2	0.2	9.2	0.2	0.2	1.3
CONI	17	0.2	0.2	6.0	0.2	0.2	1.3
CONI	18	0.2	0.2	3.4	40.0	0.2	1.5
		0.2	0.233333	7.3	6.883333	0.2	3.666666
		ERR	0.047140	3.129962	14.81062	ERR	5.292972
CONI	19	0.2	0.3	8.9	0.2	1.5	6.8
CONI	20	0.2	0.3	5.5	0.2	0.2	6.5
CONI	21	0.2	0.4	4.2	42.0	0.2	1.4
CONI	22	0.2	0.4	8.2	38.0	0.2	1.5
CONI	23	0.2	0.5	7.4	51.0	0.2	1.7
CONI	24	0.2	0.4	7.5	0.2	0.2	1.2
		0.2	0.383333	6.95	21.93333	0.416666	3.183333
		ERR	0.068718	1.609088	22.07069	0.484481	2.457245
CONI	25	0.2	0.4	5.8	0.2	0.2	1.3
CONI	26	0.2	0.4	5.6	0.2	0.2	2.2
CONI	27	0.2	0.3	4.7	0.2	0.3	2.5
CONI	28	0.2	0.3	4.3	0.2	0.2	1.4

CONI	29	0.2	0.2	4.0	0.2	0.2	0.8
CONI	30	0.2	0.3	9.2	0.2	0.2	0.9
		0.2	0.316666	5.6	0.2	0.216666	1.516666
		ERR	0.068718	1.734935	ERR	0.037267	0.630916
CONW	109	0.2	0.2	2.4	0.2	0.2	2.4
CONW	110	0.2	0.2	5.0	4.7	0.2	2.1
CONW	111	0.2	0.2	5.2	0.2	0.2	2.0
CONW	112	0.2	0.2	2.3	8.4	0.2	1.0
CONW	113	0.2	0.2	2.5	3.9	4.0	1.0
CONW	114	0.2	0.2	5.8	0.2	0.2	1.0
		0.2	0.2	3.866666	2.933333	0.833333	1.583333
		ERR	ERR	1.487354	3.064673	1.416176	0.595585
CONW	115	0.2	0.2	9.0	0.2	0.2	1.5
CONW	116	0.2	0.6	5.6	0.2	0.2	1.6
CONW	117	0.2	0.2	2.2	0.2	0.2	1.0
CONW	118	0.2	0.2	2.3	0.2	0.2	1.3
CONW	119	0.2	0.2	3.0	0.2	0.6	0.9
CONW	120	0.2	0.2	6.6	0.2	0.8	1.3
		0.2	0.266666	4.783333	0.2	0.366666	1.266666
		ERR	0.149071	2.508928	ERR	0.242670	0.249443
CONW	121	0.2	0.2	8.0	0.2	0.2	1.8
CONW	122	0.3	0.2	2.4	0.2	0.2	2.3
CONW	123	0.2	0.2	1.7	0.2	0.2	1.6
CONW	124	0.2	0.2	2.9	0.2	0.2	1.4
CONW	125	0.2	0.2	3.7	0.2	0.2	1.0
CONW	126	0.2	0.2	3.1	0.2	0.2	1.0
		0.216666	0.2	3.633333	0.2	0.2	1.516666
		0.037267	ERR	2.047491	ERR	ERR	0.456131
CONW	127	0.2	0.2	8.1	0.2	0.2	1.1
CONW	128	0.2	0.2	5.7	0.2	0.2	1.2
CONW	129	0.2	0.2	2.4	0.2	0.8	1.2
CONW	130	0.2	0.2	5.5	0.2	0.2	1.2
CONW	131	0.2	0.2	4.9	0.2	0.3	1.1
CONW	132	0.2	0.2	9.3	0.2	0.3	1.0
		0.2	0.2	5.983333	0.2	0.333333	1.133333
		ERR	ERR	2.228913	ERR	0.213437	0.074535
CONW	133	0.2	0.4	6.2	0.2	0.2	0.8
CONW	134	0.2	0.3	6.0	0.2	0.2	1.0
CONW	135	0.2	0.4	1.9	0.2	0.2	1.1
CONW	136	0.2	0.3	4.8	0.2	0.3	0.9

CONW	137	0.2	0.3	3.3	0.2	0.2	1.1
CONW	138	0.2	0.3	7.6	0.2	0.2	0.9
		0.2	0.333333	4.966666	0.2	0.216666	0.966666
		ERR	0.047140	1.903213	ERR	0.037267	0.110554
CONW	139	0.2	0.3	7.4	0.2	0.2	1.3
CONW	140	0.2	0.3	4.6	0.2	0.3	2.8
CONW	141	0.2	0.3	3.8	0.2	0.4	4.8
CONW	142	0.2	0.3	6.1	0.2	0.3	2.1
CONW	143	0.2	0.3	2.3	0.2	0.4	1.6
CONW	144	0.2	0.4	3.9	0.2	0.3	1.6
		0.2	0.316666	4.683333	0.2	0.316666	2.366666
		ERR	0.037267	1.656720	ERR	0.068718	1.189771

ug Chromium per total tissue

GROUP	ANIMAL NUMBER	LUNG	LIVER	INTEST	KIDNEY	MUSCLE	CARCASS
C3W	145	0.2	0.3	8.3	0.2	0.2	36.3
C3W	146	0.2	0.3	5.6	0.2	0.2	29.1
C3W	147	0.2	0.3	106.0	0.2	0.2	46.6
C3W	148	0.2	0.3	89.0	0.2	0.2	31.2
C3W	149	0.2	0.4	223.0	0.2	0.2	26.3
C3W	150	0.2	0.4	71.0	0.2	0.2	48.3
		0.2	0.333333	83.81666	0.2	0.2	36.32003
		ERR	0.047140	72.88786	ERR	ERR	8.444175
C3W	151	0.9	0.4	40.0	0.2	0.2	23.3
C3W	152	0.2	0.4	27.5	0.2	0.2	27.3
C3W	153	0.2	0.3	125.0	0.2	0.2	33.6
C3W	154	0.4	0.2	89.0	0.2	0.2	20.4
C3W	155	0.2	0.2	81.0	0.8	0.2	33.6
C3W	156	0.2	0.2	179.0	0.2	0.2	23.2
		0.35	0.283333	90.25	0.3	0.2	26.88300
		0.256580	0.089752	51.04552	0.223606	ERR	5.144248
C3W	157	0.2	0.3	53.0	0.2	0.2	40.3
C3W	158	0.2	0.4	38.0	0.2	0.2	34.2
C3W	159	0.2	0.3	182.0	0.2	0.2	206.3
C3W	160	0.2	0.3	129.0	0.2	0.2	65.6
C3W	161	0.2	0.3	85.0	0.2	0.2	34.8
C3W	162	0.7	0.3	186.0	0.2	0.2	102.5
		0.283333	0.309256	112.1666	0.2	0.2	80.61788
		0.186338	0.020698	58.23920	ERR	ERR	61.05419
C3W	163	0.2	0.2	66.0	0.2	0.2	28.1
C3W	164	0.2	0.2	62.0	0.2	0.3	36.6
C3W	165	0.2	0.2	245.0	0.2	0.3	65.7
C3W	166	0.2	0.2	270.0	0.2	0.3	47.5
C3W	167	0.2	0.2	105.0	0.2	0.2	48.3
C3W	168	0.2	0.2	270.0	0.2	0.2	46.0
		0.2	0.2	169.6666	0.2	0.25	45.36873
		ERR	0.000000	93.38926	ERR	0.05	11.56060
C3W	169	0.2	0.2	38.0	0.2	0.2	50.0
C3W	170	0.2	0.2	32.0	0.2	0.2	48.7
C3W	171	0.2	0.2	50.0	0.2	0.2	49.0
C3W	172	0.2	0.2	86.0	0.2	0.2	45.7

C3W	173	0.2	0.2	38.5	0.2	0.2	34.7
C3W	174	0.2	0.2	27.5	0.2	0.2	53.7
		0.2	0.2	45.33333	0.2	0.2	46.96603
		ERR	ERR	19.45864	ERR	ERR	5.983931
C3W	175	0.2	0.2	6.7	0.2	0.2	52.3
C3W	176	0.2	0.3	8.1	0.2	0.3	59.5
C3W	177	0.2	0.3	7.0	0.2	0.2	32.7
C3W	178	0.2	0.2	6.7	0.2	0.2	47.4
C3W	179	0.2	0.3	4.8	0.2	0.2	44.5
C3W	180	1.4	0.3	5.2	0.2	0.2	47.6
		0.4	0.275243	6.416666	0.2	0.216666	47.32798
		0.447213	0.054294	1.112679	ERR	0.037267	8.112943
C3I	67	3.4	0.2	71.0	0.2	0.2	24.0
C3I	68	3.2	0.2	3.6	0.2	0.2	39.5
C3I	69	4.6	0.2	12.8	0.2	0.2	54.2
C3I	70	3.2	0.2	9.8	0.2	0.2	39.9
C3I	71	3.0	0.2	23.0	0.2	0.2	30.8
C3I	72	3.2	0.2	12.2	0.2	0.2	17.5
		3.433333	0.211870	22.06666	0.2	0.2	34.30806
		0.534373	0.012627	22.62024	ERR	ERR	11.94248
C3I	37	9.0	0.2	100.0	0.2	0.2	43.4
C3I	38	8.0	0.2	10.8	0.2	0.2	29.6
C3I	39	8.4	0.2	12.6	0.2	0.2	15.5
C3I	40	7.0	0.2	7.0	0.2	0.2	18.3
C3I	41	9.8	0.2	5.6	0.2	0.2	25.1
C3I	42	8.4	0.2	4.2	0.2	0.3	24.2
		8.433333	0.2	23.36666	0.2	0.216666	26.03224
		0.859586	ERR	34.39329	ERR	0.037267	9.011887
C3I	43	16.8	0.2	112.0	0.2	0.2	47.6
C3I	44	17.6	0.2	8.8	0.2	0.2	42.1
C3I	45	17.0	0.2	4.2	0.2	0.2	23.5
C3I	46	15.6	0.2	7.0	0.2	0.2	25.4
C3I	47	18.2	0.2	10.4	0.2	0.2	33.3
C3I	48	17.4	0.2	11.4	0.2	0.2	151.2
		17.1	0.2	25.63333	0.2	0.2	53.86382
		0.806225	ERR	38.69494	ERR	ERR	44.36714
C3I	49	39.2	0.2	148.0	0.2	0.2	51.8
C3I	50	27.9	0.2	32.0	0.2	0.2	40.4
C3I	51	33.9	0.2	14.4	5.0	0.2	29.5
C3I	52	38.7	0.2	15.0	0.2	0.2	38.4

C3I	53	38.2	0.2	17.2	0.2	0.2	34.3
C3I	54	34.2	0.2	10.0	0.2	0.2	26.8
		35.35	0.201007	39.43333	1	0.2	36.87151
		3.939014	0.002251	49.03446	1.788854	ERR	8.150663
C3I	55	65.0	0.2	78.0	0.2	0.3	163.9
C3I	56	65.0	0.2	34.8	0.2	0.2	54.4
C3I	57	75.5	0.2	9.4	0.2	0.2	24.4
C3I	58	54.5	0.2	18.0	0.2	0.2	33.1
C3I	59	62.0	0.2	14.4	0.2	0.2	37.4
C3I	60	60.0	0.2	29.2	0.2	0.3	27.4
		63.66666	0.202287	30.63333	0.2	0.233333	56.78223
		6.374863	0.005115	22.86552	ERR	0.047140	48.86250
C3I	61	44.5	0.2	14.4	0.2	0.2	35.4
C3I	62	39.5	0.2	5.2	0.2	0.3	34.9
C3I	63	46.0	0.2	4.2	0.2	0.3	29.7
C3I	64	37.0	0.2	6.0	0.2	0.4	41.3
C3I	65	50.0	0.2	2.8	0.2	0.3	55.2
C3I	66	40.5	0.2	6.2	0.2	0.3	41.7
		42.91666	0.204178	6.466666	0.2	0.3	39.70275
		4.372419	0.006210	3.728568	ERR	0.057735	8.037046
C6I	103	1.9	0.2	4.9	0.2	0.2	28.2
C6I	104	1.7	0.2	8.7	0.2	0.2	16.5
C6I	105	1.8	0.2	16.5	0.2	0.2	18.8
C6I	106	2.0	0.2	13.9	0.2	0.2	16.1
C6I	107	2.2	0.2	11.7	0.2	0.2	20.6
C6I	108	2.1	0.2	9.7	0.2	0.2	18.3
		1.95	0.211635	10.9	0.2	0.2	19.74522
		0.170782	0.015468	3.725587	ERR	ERR	4.059481
C6I	73	4.1	0.4	6.0	0.2	0.2	34.1
C6I	74	5.0	0.5	7.2	0.4	0.2	30.1
C6I	75	5.4	0.5	8.0	0.5	0.2	29.1
C6I	76	3.6	0.4	7.0	0.4	0.2	24.6
C6I	77	4.2	0.5	5.1	0.4	0.2	23.9
C6I	78	8.3	0.5	3.7	0.4	0.2	20.2
		5.1	0.466666	6.166666	0.383333	0.2	27.00710
		1.549193	0.047140	1.436043	0.089752	ERR	4.603040
C6I	79	6.7	0.7	7.3	0.4	0.2	39.8
C6I	80	8.1	0.5	14.7	0.4	0.2	29.1
C6I	81	7.2	0.7	3.2	0.6	0.2	19.7
C6I	82	8.2	0.5	4.5	0.5	0.2	25.1

C6I	83	7.2	0.5	6.9	0.4	0.2	17.5
C6I	84	7.8	0.4	13.5	0.5	0.2	18.8
		7.533333	0.55	8.35	0.466666	0.2	25.02086
		0.540575	0.111803	4.308808	0.074535	ERR	7.738978
C6I	85	13.6	0.5	16.5	0.8	0.3	33.5
C6I	86	12.4	0.7	16.7	0.4	0.2	28.2
C6I	87	11.8	0.5	17.5	0.6	0.3	25.7
C6I	88	15.0	0.6	15.7	0.7	0.4	32.2
C6I	89	13.0	0.7	13.1	0.8	0.3	22.1
C6I	90	14.2	0.5	11.1	0.8	0.3	33.6
		13.33333	0.583333	15.1	0.683333	0.3	29.20518
		1.074967	0.089752	2.259793	0.146249	0.057735	4.299398
C6I	91	25.5	0.7	22.2	4.2	0.6	57.2
C6I	92	26.0	0.7	22.2	0.6	0.4	75.3
C6I	93	20.8	1.0	17.4	1.0	0.4	41.6
C6I	94	22.0	1.0	16.6	0.8	0.4	32.2
C6I	95	24.5	0.9	17.0	0.9	0.6	143.4
C6I	96	26.9	0.8	21.2	0.8	0.3	43.5
		24.28333	0.856069	19.43333	1.383333	0.45	65.51288
		2.185876	0.124308	2.466891	1.265459	0.111803	37.40707
C6I	97	12.0	0.4	7.5	0.3	0.2	37.4
C6I	98	15.4	0.4	6.1	0.3	0.3	43.4
C6I	99	12.6	0.4	7.1	0.3	0.2	38.2
C6I	100	10.8	0.3	5.3	0.3	0.2	26.6
C6I	101	11.4	0.4	2.3	0.5	0.2	36.1
C6I	102	15.8	0.5	4.2	0.6	0.3	28.3
		13	0.405876	5.416666	0.383333	0.233333	35.00676
		1.921804	0.039053	1.772396	0.121335	0.047140	5.814239
C6W	181	0.2	1.3	46.0	0.3	0.2	35.3
C6W	182	0.2	1.1	42.0	0.3	0.2	18.6
C6W	183	0.2	1.6	86.0	0.5	0.2	38.4
C6W	184	0.2	1.9	89.0	0.5	0.2	31.7
C6W	185	0.2	1.9	180.0	0.5	0.2	49.8
C6W	186	0.2	1.7	90.0	0.5	0.5	72.3
		0.2	1.583333	88.83333	0.433333	0.25	41.02398
		ERR	0.296741	45.36671	0.094280	0.111803	16.75870
C6W	187	0.2	3.1	53.0	0.8	0.2	42.4
C6W	188	0.2	2.6	15.3	0.8	0.2	28.9
C6W	189	0.2	3.9	279.0	2.2	0.2	49.9
C6W	190	0.2	2.2	53.0	0.9	0.2	32.9

C6W	191	0.2	3.6	130.0	1.0	0.2	38.5
C6W	192	0.4	3.8	202.0	1.3	0.3	77.9
		0.233333	3.193523	122.05	1.166666	0.216666	45.09977
		0.074535	0.631008	93.11272	0.492160	0.037267	16.12439
C6W	193	0.2	5.3	106.5	1.6	0.2	49.4
C6W	194	0.2	6.5	46.0	2.2	0.2	49.0
C6W	195	0.2	4.5	43.5	1.7	0.2	53.3
C6W	196	0.2	6.3	74.5	6.2	0.2	29.4
C6W	197	0.2	3.8	126.0	5.6	0.2	61.5
C6W	198	0.2	5.2	107.0	2.0	0.2	73.5
		0.2	5.269091	83.91666	3.216666	0.2	52.68239
		ERR	0.936273	31.55341	1.915216	ERR	13.38028
C6W	199	0.2	6.9	43.5	2.6	0.3	40.3
C6W	200	2.9	11.4	76.0	3.1	0.4	75.0
C6W	201	0.5	11.7	291.0	3.8	0.4	54.6
C6W	202	0.3	8.4	218.0	5.0	0.6	56.6
C6W	203	2.7	14.2	301.0	4.3	0.7	89.9
C6W	204	0.4	9.9	124.0	3.0	0.5	147.4
		1.166666	10.41236	175.5833	3.633333	0.483333	77.28584
		1.159980	2.361097	100.7250	0.825967	0.134370	35.10765
C6W	205	0.5	12.9	66.0	4.4	1.0	120.5
C6W	206	0.7	17.4	57.0	4.4	0.7	71.3
C6W	207	0.6	12.4	27.0	4.4	0.9	83.5
C6W	208	0.7	14.9	28.0	5.1	0.9	74.8
C6W	209	0.7	16.0	51.0	4.8	0.7	59.6
C6W	210	0.7	12.3	38.0	4.8	0.9	82.9
		0.65	14.31331	44.5	4.65	0.85	82.10957
		0.076376	1.936647	14.61449	0.269258	0.111803	18.96802
C6W	211	0.5	5.5	10.1	2.1	0.8	116.1
C6W	212	0.4	5.4	4.3	1.5	0.5	97.3
C6W	213	0.4	3.9	4.5	1.2	0.5	91.3
C6W	214	0.5	5.3	2.6	1.4	0.7	74.7
C6W	215	0.4	6.0	5.1	2.2	0.7	64.3
C6W	216	0.5	5.8	7.7	1.8	0.7	63.9
		0.45	5.315205	5.716666	1.7	0.65	84.63093
		0.05	0.675984	2.474144	0.365148	0.111803	18.86944
CONI	31	0.2	0.4	4.0	0.2	0.2	24.9
CONI	32	0.2	0.5	5.6	0.2	0.2	59.9
CONI	33	0.2	0.3	13.4	0.2	0.2	42.5
CONI	34	0.2	0.3	13.6	0.2	0.2	35.4

CONI	35	0.2	0.4	17.0	0.2	0.2	32.6
CONI	36	0.2	0.2	9.2	0.2	0.2	25.4
		0.2	0.360372	10.46666	0.2	0.2	36.80614
		ERR	0.089641	4.622649	ERR	ERR	11.96234
CONI	1	0.2	0.4	3.6	0.2	0.2	19.6
CONI	2	0.2	0.3	2.6	0.2	0.2	21.5
CONI	3	0.2	0.3	1.7	0.2	0.2	13.0
CONI	4	0.2	0.4	1.8	0.2	0.2	16.9
CONI	5	0.2	0.3	3.2	0.2	0.2	24.8
CONI	6	0.2	0.3	4.7	0.2	0.2	15.2
		0.2	0.333333	2.933333	0.2	0.2	18.48868
		ERR	0.047140	1.045094	ERR	ERR	3.959625
CONI	7	0.2	0.2	2.2	0.2	0.2	71.1
CONI	8	0.2	0.2	6.4	0.2	0.2	64.7
CONI	9	0.2	0.2	7.4	0.2	0.2	112.1
CONI	10	0.2	0.2	4.6	0.2	2.0	37.5
CONI	11	0.2	0.2	7.4	0.2	0.2	31.2
CONI	12	0.2	0.2	1.5	0.2	0.2	29.1
		0.2	0.2	4.916666	0.2	0.5	57.62172
		ERR	ERR	2.369540	ERR	0.670820	29.18462
CONI	13	0.2	0.2	6.2	0.5	0.2	411.6
CONI	14	0.2	0.3	13.2	0.2	0.2	32.9
CONI	15	0.2	0.4	5.8	0.2	0.2	31.5
CONI	16	0.2	0.2	9.2	0.2	0.2	29.8
CONI	17	0.2	0.2	6.0	0.2	0.2	29.6
CONI	18	0.2	0.2	3.4	40.0	0.2	29.4
		0.2	0.241666	7.3	6.883333	0.2	94.11550
		ERR	0.060667	3.129962	14.81062	ERR	141.9673
CONI	19	0.2	0.3	8.9	0.2	1.5	158.8
CONI	20	0.2	0.4	5.5	0.2	0.2	222.6
CONI	21	0.2	0.4	4.2	42.0	0.2	34.0
CONI	22	0.2	0.4	8.2	38.0	0.2	39.3
CONI	23	0.2	0.5	7.4	51.0	0.2	39.0
CONI	24	0.2	0.4	7.5	0.2	0.2	31.4
		0.2	0.399831	6.95	21.93333	0.416666	87.51149
		ERR	0.057736	1.609088	22.07069	0.484481	75.29433
CONI	25	0.2	0.4	5.8	0.2	0.2	34.6
CONI	26	0.2	0.4	5.6	0.2	0.2	60.7
CONI	27	0.2	0.3	4.7	0.2	0.3	68.2
CONI	28	0.2	0.3	4.3	0.2	0.2	36.5

CONI	29	0.2	0.2	4.0	0.2	0.2	23.9
CONI	30	0.2	0.3	9.2	0.2	0.2	27.5
		0.2	0.319117	5.6	0.2	0.216666	41.89246
		ERR	0.068341	1.734935	ERR	0.037267	16.64055
CONW	109	0.2	0.2	2.4	0.2	0.2	37.8
CONW	110	0.2	0.2	5.0	4.7	0.2	27.0
CONW	111	0.2	0.2	5.2	0.2	0.2	26.8
CONW	112	0.2	0.2	2.3	8.4	0.2	13.5
CONW	113	0.2	0.2	2.5	3.9	4.0	19.3
CONW	114	0.2	0.2	5.8	0.2	0.2	18.9
		0.2	0.200812	3.866666	2.933333	0.833333	23.87368
		ERR	0.001816	1.487354	3.064673	1.416176	7.813874
CONW	115	0.2	0.2	9.0	0.2	0.2	28.2
CONW	116	0.2	0.6	5.6	0.2	0.2	28.6
CONW	117	0.2	0.2	2.2	0.2	0.2	14.9
CONW	118	0.2	0.2	2.3	0.2	0.2	24.4
CONW	119	0.2	0.2	3.0	0.2	0.6	15.3
CONW	120	0.2	0.2	6.6	0.2	0.8	18.4
		0.2	0.266666	4.783333	0.2	0.366666	21.62413
		ERR	0.149071	2.508928	ERR	0.242670	5.708423
CONW	121	0.2	0.2	8.0	0.2	0.2	45.4
CONW	122	0.3	0.2	2.4	0.2	0.2	51.1
CONW	123	0.2	0.2	1.7	0.2	0.2	32.3
CONW	124	0.2	0.2	2.9	0.2	0.2	25.2
CONW	125	0.2	0.2	3.7	0.2	0.2	18.5
CONW	126	0.2	0.2	3.1	0.2	0.2	19.7
		0.216666	0.2	3.633333	0.2	0.2	32.01610
		0.037267	0.000000	2.047491	ERR	ERR	12.40866
CONW	127	0.2	0.2	8.1	0.2	0.2	30.1
CONW	128	0.2	0.2	5.7	0.2	0.2	33.7
CONW	129	0.2	0.2	2.4	0.2	0.8	27.8
CONW	130	0.2	0.2	5.5	0.2	0.2	28.8
CONW	131	0.2	0.3	4.9	0.2	0.3	24.6
CONW	132	0.2	0.2	9.3	0.2	0.3	21.1
		0.2	0.210352	5.983333	0.2	0.333333	27.68431
		ERR	0.023148	2.228913	ERR	0.213437	4.018679
CONW	133	0.2	0.4	6.2	0.2	0.2	24.8
CONW	134	0.2	0.3	6.0	0.2	0.2	34.1
CONW	135	0.2	0.4	1.9	0.2	0.2	26.5
CONW	136	0.2	0.3	4.8	0.2	0.3	24.6

CONW	137	0.2	0.3	3.3	0.2	0.2	29.8
CONW	138	0.2	0.3	7.6	0.2	0.2	23.0
		0.2	0.338875	4.966666	0.2	0.216666	27.12122
		ERR	0.050331	1.903213	ERR	0.037267	3.749588
CONW	139	0.2	0.3	7.4	0.2	0.2	54.6
CONW	140	0.2	0.3	4.6	0.2	0.3	76.2
CONW	141	0.2	0.3	3.8	0.2	0.4	98.9
CONW	142	0.2	0.3	6.1	0.2	0.3	52.8
CONW	143	0.2	0.3	2.3	0.2	0.4	31.1
CONW	144	0.2	0.4	3.9	0.2	0.3	37.7
		0.2	0.316666	4.683333	0.2	0.316666	58.56690
		ERR	0.037267	1.656720	ERR	0.068718	22.99807

GROUP	ANIMAL NUMBER	METABOLISM CAGE DATA: URINE IN ml TOTAL	FOR CREAT	URINE CHROMIUM AND CREATININE DATA: URINE Cr ng/ml	URINE CREAT mg/ml	URINE Cr/CREAT	URINE Cr mg/da	MEAN URINE Cr mg/da
C3W	145	11.77	1	16.7	0.52	0.000032	0.000289	
C3W	146	8.30	1	13.8	0.75	0.000018	0.000165	0.000227
C3W	147							
C3W	148							
C3W	149							
C3W	150							
C3W	151	5.02	1	9.8	1.3	0.000007	0.000067	
C3W	152	12.47	1	3.7	0.52	0.000007	0.000064	0.000065
C3W	153							
C3W	154							
C3W	155							
C3W	156							
C3W	157	11.3[illegible]	1	1.0	0.85	0.000001	0.000010	
C3W	158	17.96	1	6.2	0.8	0.000007	0.000069	0.000040
C3W	159							
C3W	160							
C3W	161							
C3W	162							
C3W	163	11.67	1	1.4	0.8	0.000001	0.000015	
C3W	164	20.24	1	7.8	0.52	0.000015	0.000135	0.000075
C3W	165							
C3W	166							
C3W	167							
C3W	168							
C3W	169	16.80	1	2.3	0.85	0.000002	0.000024	
C3W	170	15.81	1	0.9	0.75	0.000001	0.000010	0.000017
C3W	171							
C3W	172							
C3W	173							
C3W	174							

C3W	175	10.58	1	0.0	0.65	0	0	
C3W	176	13.82	1	0.0	0.8	0	0	0
C3W	177							
C3W	178							
C3W	179							
C3W	180							
C3I	67	13.72	17.9	15.4	0.45	0.000034	0.000308	
C3I	68	4.00	1	17.9	1.3	0.000013	0.000123	0.000215
C3I	69							
C3I	70							
C3I	71							
C3I	72							
C3I	37	14.71	1	11.9	0.55	0.000021	0.000194	
C3I	38	16.65	1	0.4	0.45	0.000000	0.000008	0.000101
C3I	39							
C3I	40							
C3I	41							
C3I	42							
C3I	43	14.71	1	6.9	0.7	0.000009	0.000088	
C3I	44	16.00	1	5.8	0.65	0.000008	0.000080	0.000084
C3I	45							
C3I	46							
C3I	47							
C3I	48							
C3I	49	17.04	1	4.3	0.75	0.000005	0.000051	
C3I	50	16.95	1	0.9	0.6	0.000001	0.000013	0.000032
C3I	51							
C3I	52							
C3I	53							
C3I	54							
C3I	55	10.63	1	0.7	1.2	0.000000	0.000005	
C3I	56	16.23	1	0.0	0.9	0	0	0.000002

C3I	57							
C3I	58							
C3I	59							
C3I	60							
C3I	61	4.09	1	0.0	2.4	0	0	
C3I	62	21.14	1	0.3	0.75	0.000000	0.000003	0.000001
C3I	63							
C3I	64							
C3I	65							
C3I	66							
C6I	103	16.59	1	19.5	0.38	0.000051	0.000461	
C6I	104	16.95	1	20.6	0.32	0.000064	0.000579	0.000520
C6I	105							
C6I	106							
C6I	107							
C6I	108							
C6I	73	17.42	1	9.5	0.35	0.000027	0.000244	
C6I	74	11.11	1	17.7	0.93	0.000019	0.000171	0.000207
C6I	75							
C6I	76							
C6I	77							
C6I	78							
C6I	79	15.02	1	13.5	0.75	0.000018	0.000162	
C6I	80	25.89	1	16.5	0.4	0.000041	0.000371	0.000266
C6I	81							
C6I	82							
C6I	83							
C6I	84							
C6I	85	7.93	1	9.9	1.2	0.000008	0.000074	
C6I	86	11.02	1	19.0	0.87	0.000021	0.000196	0.000135
C6I	87							
C6I	88							
C6I	89							
C6I	90							

C6I	91	1.76		13.9	4.2	0.000003	0.000029	
C6I	92	4.88		15.8	2.2	0.000007	0.000064	0.000047
C6I	93							
C6I	94							
C6I	95							
C6I	96							
C6I	97	6.42	1	0.8	1.05	0.000000	0.000006	
C6I	98	4.96	1	3.9	1.9	0.000002	0.000018	0.000012
C6I	99							
C6I	100							
C6I	101							
C6I	102							
C6W	181	36.02	1	40.1	2.6	0.000015	0.000138	
C6W	182	9.74	1	55.3	0.45	0.000122	0.001106	0.000622
C6W	183							
C6W	184							
C6W	185							
C6W	186							
C6W	187	13.13	1	90.0	0.65	0.000138	0.001246	
C6W	188	22.42	1	90.4	0.35	0.000258	0.002324	0.001785
C6W	189							
C6W	190							
C6W	191							
C6W	192							
C6W	193	17.91	1	117.0	1.4	0.000083	0.000752	
C6W	194	36.68	1	127.0	0.35	0.000362	0.003265	0.002008
C6W	195							
C6W	196							
C6W	197							
C6W	198							

C6W	199	28.88	1	114.0	0.35	0.000325	0.002931	
C6W	200	13.70	1	162.0	0.45	0.00036	0.00324	0.003085
C6W	201							
C6W	202							
C6W	203							
C6W	204							
C6W	205	28.46	1	177.0	0.52	0.000340	0.003063	
C6W	206	14.16	1	117.0	0.8	0.000146	0.001316	0.002189
C6W	207							
C6W	208							
C6W	209							
C6W	210							
C6W	211	26.76	1	21.0	0.67	0.000031	0.000282	
C6W	212	14.09	1	18.8	1.1	0.000017	0.000153	0.000217
C6W	213							
C6W	214							
C6W	215							
C6W	216							
CONI	31	8.44	1	5.3	0.7	0.000007	0.000068	
CONI	32	10.28	1	1.4	0.72	0.000001	0.000017	0.000042
CONI	33							
CONI	34							
CONI	35							
CONI	36							
CONI	1	19.19	1	0.0	0.3	0	0	
CONI	2	6.82	1	0.3	0.7	0.000000	0.000003	0.000001
CONI	3							
CONI	4							
CONI	5							
CONI	6							
CONI	7	10.28	1	0.0	0.8	0	0	
CONI	8	9.26	1	0.0	0.93	0	0	0
CONI	9							
CONI	10							

CONI	11							
CONI	12							
CONI	13	11.32	1	0.0	0.95	0	0	
CONI	14	14.60	1	0.0	0.72	0	0	0
CONI	15							
CONI	16							
CONI	17							
CONI	18							
CONI	19	10.18	1	0.0	0.87	0	0	
CONI	20	8.13	1	0.0	1.3	0	0	0
CONI	21							
CONI	22							
CONI	23							
CONI	24							
CONI	25	9.38	1	0.0	1.4	0	0	
CONI	26	12.68	1	0.1	0.95	0.000000	0.000000	0.000000
CONI	27							
CONI	28							
CONI	29							
CONI	30							
CONW	109	21.58	1	1.0	0.4	0.000002	0.000022	
CONW	110	8.87	1	1.2	0.85	0.000001	0.000012	0.000017
CONW	111							
CONW	112							
CONW	113							
CONW	114							
CONW	115	13.78	1	0.0	0.3	0	0	
CONW	116	7.85	1	0.0	1.05	0	0	0
CONW	117							
CONW	118							
CONW	119							
CONW	120							

CONW	121	16.66	1	0.9	1.05	0.000000	0.000007	
CONW	122	10.56	1	0.0	0.85	0	0	0.000003
CONW	123							
CONW	124							
CONW	125							
CONW	126							
CONW	127	10.31	1	0.0	1.05	0	0	
CONW	128	13.59	1	0.0	0.52	0	0	0
CONW	129							
CONW	130							
CONW	131							
CONW	132							
CONW	133	18.38	1	0.0	0.75	0	0	
CONW	134	4.67	1	4.7	2.1	0.000002	0.000020	0.000010
CONW	135							
CONW	136							
CONW	137							
CONW	138							
CONW	139	30.00	1	0.0	0.27	0	0	
CONW	140	6.62	1	0.0	2	0	0	0
CONW	141							
CONW	142							
CONW	143							
CONW	144							

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